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14. ABSTRACT
Gulf War (GW) veterans continue to complain of short-term memory and mood problems many years after their deployment. Suspected causes for these complaints include additive and/or synergystic effects of the varying combinations of exposures to pesticides, pyridostigmine bromide (PB), low-level nerve agents, and psychological trauma. Many pesticides are neurotoxicants as are PB and nerve agents. Two subsets of these chemicals, organophosphates (OP) and carbamates, are known to produce chronic neurological symptoms at sufficient exposure levels. It was the goal of this study to further evaluate the role of pesticides in the development of symptoms reported by GW veterans. This was accomplished by performing neuropsychological assessments with a group of military pesticide applicators. It was hypothesized that pesticide applicators with higher exposures would perform significantly worse on cognitive and neurological measures than a group of GW military personnel with very little pesticide exposure and that multiple chemical exposures (PB, pesticides) would prove synergistic in terms of decreased cognitive and neurological functioning and increased physical symptoms. Study results showed that the multiple exposed group (PB, pest) performed worse on information processing speed and reported increased mood complaints and health symptoms compared with the other exposure groups. The high pesticide group also performed worse on visual memory functioning.

15. SUBJECT TERMS
Neurotoxicant exposures, neuropsychological deficits, Gulf War veterans, central nervous system, pesticides, pyridostigmine bromide.

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INTRODUCTION

Gulf War (GW) veterans continue to complain of short-term memory and mood problems many years following their return from the Persian Gulf. Research to date suggests that it is unlikely that there is one single cause for the health complaints dating to service in the Gulf. It appears that there are multiple etiologies of these complaints and that causation may vary among GW veterans. Suspected causes for GW veterans continued health complaints include additive and/or synergystic effects of varying combinations of exposures to pesticides, pyridostigmine bromide (PB), low-level nerve agents, and psychological trauma. In our lab, research evaluating the effects of pyridostigmine bromide (PB) exposure on neuropsychological functioning in GW veterans, found significantly lower performance on a task assessing executive system functioning in the PB exposed GW veterans compared with controls (Sullivan et al., 2003). Pesticide exposure was associated with mood decrements and residual symptom effects many years after exposure in a large longitudinal cohort of GW veterans also studied by our group (White et al., 2001). In addition, potential low-level nerve agent exposure (from Khamisiyah weapons arsenal) was associated with mood complaints and executive system decrements in GW veterans (White et al., 2001) and with motor and visuospatial decrements (Proctor et al., 2006) in a dose-dependent manner.

Many pesticides are neurotoxicants as are PB and nerve agents. Two subsets of these chemicals, organophosphates (OP) and carbamates, are known to produce chronic neurological symptoms with sufficient exposure. For example, studies of agricultural workers and professional pesticide applicators have found lasting decrements in neurological and cognitive functioning resulting in decreased information processing speed and increased mood complaints (Bazylewicz-Walcczak et al., 1999; Stephens et al., 1995; Steenland et al., 1994), with chronic low-level exposures as well as with acute poisoning.

It was the goal of this study to further evaluate the role of pesticides in the development of CNS symptoms reported by GW veterans and to assess the additive and/or synergistic effects of combinations of chemical exposures and stress. This was accomplished by assessing a group of military pesticide applicators with known chemical exposures. It was hypothesized that applicators with high exposures would perform significantly worse on specific cognitive and neurological measures and report more health symptom complaints than a group of GW military personnel with very little pesticide exposure. It was also hypothesized that multiple chemical exposures (PB, pesticides, low-level nerve agents) would be synergistic and/or additive in their effects on decreased cognitive and neurological functioning.

The specific aims of this study are: (1) To determine the cognitive and neurological effects of pesticide exposure in specific groups of GW veterans (2) To determine the cognitive and neurological effects of PB exposure in specific groups of pesticide exposed GW veterans (3) To assess for interaction effects in GW veterans with multiple chemical exposures (PB, pesticides, low-level nerve agents).

BODY

The approved statement of work for the entire study period is below:

STATEMENT OF WORK

Neuropsychological Functioning in Gulf War Veterans Exposed to Pesticides and Pyridostigmine Bromide.

Task 1. Develop Plan for Subject Recruitment Months 1-6:

a. Locate and obtain previous exposure interviews from a group of Gulf War veteran pest-control interviewees (PCI) previously contacted by Office of the Special Assistant to the Under Secretary of Defense for GW illnesses (OSA) in 1997-1998 (months 1-3).
b. SRBI, an independent contracting company (with an 80% success rate) will contact all PCIs and obtain current address and administer a brief follow-up questionnaire (months 3-4).
c. Categorize PCIs into high and low exposure groups for pesticides and pyridostigmine bromide (PB) exposure (months 3-5).
d. Identify pool of potential subjects for each of four exposure categories to recruit (months 4-5).
e. Screen potential subjects for exclusion criteria (months 5-6).

Task 2. Perform Subject Recruitment and Data Collection Months 6-42:

a. Study coordinator will contact potential subjects for recruitment and arrange for travel to multiple study sites (months 6-42).
b. Perform cognitive evaluations and psychodiagnostic interviews from 160 study participants (months 6-42).
c. Obtain information about current health status, environmental and occupational exposures, medical or psychological treatments, and any recent medical or psychiatric diagnoses for all study subjects (months 6-42).

Task 3. Data Collection and Interim Analyses, Months 18-42:

a. Data entry of all questionnaires and evaluations and quality control measures will be ongoing (months 18-42).
b. Interim Statistical analyses of data obtained from cognitive evaluations and questionnaire data will be performed periodically (months 18-42).
c. Exposure assessment analyses for pesticides and PB will be ongoing (months 18-42).
d. Annual reports of progress will be written (12-36).

Task 4. Final Analysis and Report Writing, Months 42-48:

a. Analyze subject characteristics of individuals who were lost to follow-up (months 42-44).
b. Write final study report and prepare manuscripts for submission (months 44-48).

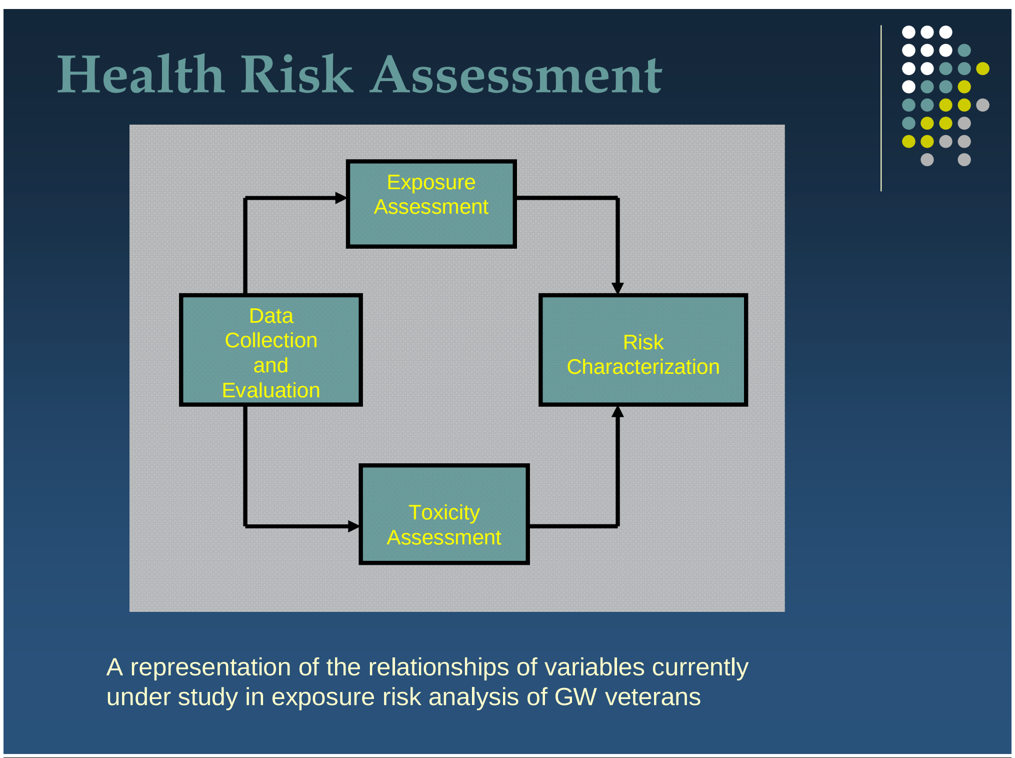
The statement of work for years 1-4 is below. The statement of work for year 1 primarily describes the completion of the start-up phase of the study including obtaining the study sample from a group of pest control interviewees (PCIs) previously interviewed by the Deployment Health Support Directorate (DHSD), to obtain current contact information for the PCIs and administer a brief follow-up questionnaire with these individuals. In year 2, the plan was to recruit 58 study participants for the study protocol including cognitive evaluations, psychological interviews and exposure questionnaires and perform data entry and cleaning, and preliminary analyses of the data. The total recruitment for year 2 was 47 study participants. The recruitment goal for year 3 included 61 study participants (50 for the initial projections and 11 from the year 2 goal). The total recruitment for year 3 was 60 study participants. The recruitment goal for year 4 was 41 study participants for a total of 160 subjects. The total recruitment for year 4 was 40 study participants bringing the total study recruitment to 159 study participants (99% recruitment goal). A no-cost 6-month extension was granted in order to complete data analyses and this final report.

Task 1a. Locate and obtain records of PCI surveys from the Deployment Health Support Directorate (formerly OSAGWI) conducted in 1997-1998.

The Pesticides Environmental Exposure Report (www.gulflink.osd.mil) commissioned by the Deployment Health Support Directorate provided estimates of exposure for general deployed military and separately for pesticide applicators from the Gulf War based on interviews with the current study sample of pesticide applicators and preventive medicine specialists and a review of DOD pesticide records known collectively as a health risk assessment (Figure 1). The health risk assessement was performed by relying on interviews with veterans and researching military pesticide records to develop pesticide exposure scenarios. These exposure scenarios were then used to estimate potential health risks following a four-step methodology adapted by Mr. Bradford from the procedures used in the Environmental Protection Agency, Office of pesticide programs (EPA/OPP (see figure 1). The four-step procedure for determining potential health risks

included data collection and evaluation, exposure assessment, toxicity assessment and risk characterization. Data Collection and Evaluation included the gathering and analyzing of background information from a variety of sources including military records (logistics information, preventive medicine records, message traffic, and unit records) and pesticide references. The Exposure Assessment determined which specific pesticides were applied, identifying who was exposed, identifying the way in which they were exposed, and estimating how much exposure they experienced. The Toxicity Assessment included establishing a given pesticide's potential for causing adverse health effects and the Risk Characterization described the potential for adverse health effects by combining information from the exposure assessment and toxicity assessment.

Figure 1. Health Risk Assessment for assessing Pesticide Exposure risk in GW veterans.



The term "pest control interviewee" (PCI) refers to any of the 298 personnel interviewed by the Office of the Special Assistant for Gulf War Illnesses (OSAGWI) in the course of the "preventive medicine" (PM), "delousing," and other interviews described in OSAGWI's Pesticides Environmental Exposure Report. OSAGWI chose to interview these individuals because it was believed that they would be the most likely to have knowledge of pesticide products used in the Army, Navy, Air Force, and Marines. They were identified based on military occupational specialty (MOS) codes. PCIs include physicians, entomologists, environmental science officers, preventive medicine specialists, field sanitation team members, military police, and other pest controllers. OSAGWI has since been renamed the Deployment Health Support Directorate (DHSD) and then Force Health Protection and Readiness Programs (FHP & RP).

The current study is an examination of the CNS effects of neurotoxicant exposure in pest control interviewees (PCI) with known neurotoxicant exposures as a result of their tour of duty at the time of the Gulf War. PCI's comprise specific groups of GW veterans likely to fall into high and low categories of pesticide exposure based on their military occupational specialty (MOS) or designation. Each potential participant previously completed a pesticide interview that included self-report measures of exposures to neurotoxicants while in the Gulf region. PCI contact information and interview data (conducted in 1997-1998) were provided to the Principal Investigator by Dr. Michael Kilpatrick, M.D., Deputy Director of the Force Health Protection and Readiness Programs (previously known as OSAGWI and Deployment Health Support Directorate) through their System of Records Notice which permits release of records to the Veterans Administration. The DHSD released the records to the VA Boston Healthcare System through a Memorandum of Understanding (MOU). The MOU provided assurances from the VA Boston Healthcare System and the Boston Environmental Hazards Center (a joint program of the VA Boston Healthcare System and Boston University).

The MOU states:

1) The released PCI records will only be used for the purposes of the current study

2) Only study personnel will have access to the released records

3) The released information will be safeguard to preserve the confidentiality of the data

4) Any personal identifiers will be removed from any interim and final reports that are prepared as a consequence of this study.

The PCI interview records were used in conjunction with current interview data collected during the study to categorize individuals into high and low pesticide and PB (pyridostigmine bromide) exposure categories. In addition, these interviews have also been used in conjunction with the current exposure questionnaires to perform a health risk assessment for pesticides and PB. Mr. William Bradford, lead author of the Environmental Exposure Report-Pesticides, assisted with these dose-estimates.

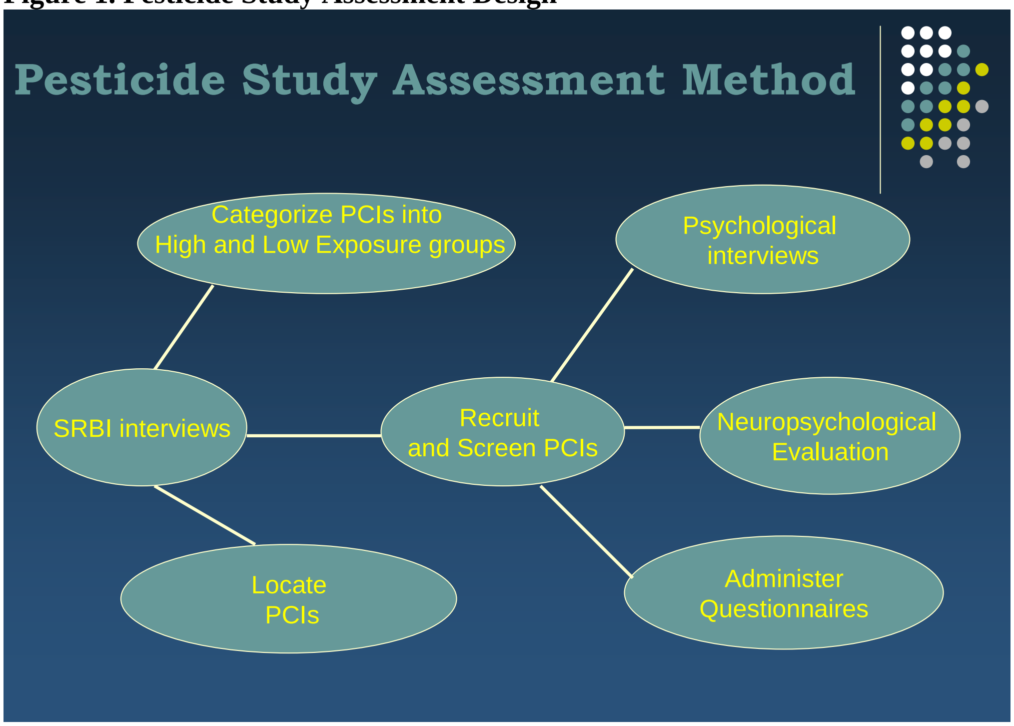
Task 1b. SRBI, an independent contracting company will contact PCIs and obtain current address and administer a brief follow-up questionnaire.

An outside research firm (Schulman, Ronca, & Bucuvalas, Inc., SRBI) with extensive experience collecting data from veterans of the U.S. Armed Forces was subcontracted to obtain current telephone numbers and addresses for the PCIs and to administer a brief follow-up questionnaire by telephone. The recruitment process was as follows: PCIs were sent a letter from the PI explaining that SRBI would be contacting them to conduct a brief telephone interview and obtain their current contact information for the study. A postage paid opt-out postcard was included with this introduction letter. If the PCI elected to return this postcard, there was no further contact with this individual for the study. If a postcard was not returned to the study staff, SRBI attempted to contact the PCI and determine if they wished to participate in the brief interview regarding pesticide and PB exposures during the Gulf War. Ten individuals returned the opt-out postcards and were not contacted further for this study. From the remaining list, SRBI

was successful in completing 160 telephone interviews with PCIs regarding neurotoxicant exposures, resulting in a live refusal rate of just 7 %. SRBI was also able to find current contact information for all 293 PCIs and conclude that one PCI was deceased.

The study design is presented in the figure below followed by tables of demographic information computed from the SRBI telephone interview data.

Figure 1. Pesticide Study Assessment Design



From the SRBI telephone interviews, demographic and exposure data was collected from each responding PCI. The demographic information is reported in Table 1. From this group of 160 study respondents, 140 were male and 20 were female. The average age for the group of Gulf War veterans was 48 years old and the group was largely Caucasian (85%). The most commonly reported current health problems reported by these study participants were hypertension, cardiovascular disease, arthritis, asthma, back and joint pain, skin rash and memory problems. When broken down into groups based on high and low exposure to pesticides or PB, the only notable differences were found in increased reporting of hypertension (12 vs. 6 PCIs), cardiovascular disease (6 vs. 2 PCIs) and arthritis (6 vs. 1 PCI) in the high pesticide group

compared with the low pesticide group. The high and low PB groups did not appear to differ with respect to health symptom reporting from this brief health query included in the telephone interviews. The larger study questionnaire with more in-depth questions regarding medical diagnoses have better characterized these groups in terms of health outcomes and shown their significance. The demographic breakdown of the SRBI surveys is reported in table 1.

Table 1. Demographic Breakdown for SRBI Survey Respondents		
Gender	Frequency	Percent
Male	140	87.5
Female	20	12.5
Total	160	100

Current Age for SRBI Survey Respondents		
Minimum	Maximum	Mean
33	74	48

Ethnicity for SRBI Survey Respondents		
Ethnicity	Frequency	Percent
African American	12	7.5
Asian American	3	1.9
Caucasian	136	85.0
Hispanic American	6	3.8
Other	3	1.9

Health Symptom Self-report for SRBI Respondents		
Symptom	Frequency	Percent
Hypertension	23	14
Cardiovascular Disease	11	7
Arthritis	12	8
Asthma	10	6
Back Pain	11	7
Joint Pain	13	8
Skin Rash	14	9
Memory Problems	14	9

Task 1c. Categorize PCIs into high and low exposure groups for pesticides and pyridostigmine bromide (PB) exposure.

Pesticides were used widely in the Gulf War to protect troops from pests such as sand flies, mosquitoes and fleas that can carry the infectious diseases leishmaniasis, sand fly fever and malaria. Of the nearly 700,000 US troops deployed to the Gulf region, only 40 cases of infectious diseases were documented (Winkenwerder Jr, W., 2003). US forces used pesticides in areas where they worked, slept, and ate throughout the GW. In fact, on any given day during their deployment, GW troops could have been exposed to 15 pesticide products with 12 different active ingredients. Pesticide applicators were likely exposed to more pesticide products and at higher doses. Troops used pesticides for a number of reasons, including personal use on the skin and uniforms as an insect repellent, as area sprays and fogs to kill flying insects, in pest strips and fly baits to attract and kill flying insects, and as delousing agents applied to enemy prisoners of war.

These widespread, commonly reported uses supported the decision by the OSAGWI to investigate pesticide exposures as a potential contributor to unexplained illnesses in GW veterans. According to the OSAGWI report, the pesticides of potential concern (POPCs) used by US military personnel during the GW can be divided into five major classes or categories: 1) organophosphorus pesticides (OP), such as dichlorvos, malathion, and chlorpyrifos; 2) carbamate pesticides, such as bendiocarb; 3) the organochlorine, lindane; 4) pyrethroid pesticides, such as permethrin; and 5) the insect repellent DEET (see figures 2 through 4). The Environmental Exposure Report – Pesticides (www.GulfLINK.osd.mil) concluded that 41,000 general military personnel could have had some over-exposure to pesticides based on the health risk assessment dose-estimates (Figure 4) and that the acetylcholinesterase (AchE) inhibiting pesticides (including organophosphates and carbamates) could be among the contributing factors to some of the undiagnosed illnesses in GWI veterans.

A recent review of thousands of pesticides as part of the Food Quality Protection Act by the Environmental Protection Agency (EPA) has resulted in the re-evaluation of the safety of some OP pesticides, causing recommendations for the restricted use or banning of several of the most commonly used chemicals. These include chlorpyrifos, diazinon, malathion and dichlorvos. As part of this sweeping pesticide review, the EPA also suggested that some OP pesticides may have endocrine disrupting properties at doses much lower than would cause acute cholinergic effects. For example, malathion was reported to affect thyroid functioning and to be associated with thyroid tumors in this report (www.epa.gov/pesticides/cumulative/rra-op). Diazinon was also reported to be associated with delayed bone growth, abnormal bone cysts and decreased bone mineral density in a separate report (Dahlgren et al., 2004). In addition, the organochlorine lindane has also been severely restricted by EPA because of its persistence in the environment, ability to bioaccumulate, potential as a carcinogen and evidence as an endocrine disruptor (http://www.epa.gov/oppsrrd1/reregistration/REDs/lindane_red_addendum.pdf).

Figure 2. Pesticide Use and Application Overview.

Pesticide Use and Application Overview

Use	Designation	Purpose	POPCs, Active Ingredient	Application Method	User or Applicator
General Use Pesticides	Repellents	Repel flies and mosquitoes	DEET 33% cream/stick	By hand to skin	Individuals
			DEET 75% Liquid	By hand to skin, uniforms or netting	
			Permethrin 0.5% (P) Spray	Sprayed on uniforms	
	Area Spray	Knock down spray, kill files and mosquitoes	d-Phenothrin 0.2% (P) Aerosol	Sprayed in area	
	Fly Baits	Attract and kill flies	Methomyl 1% (C) Crystals	Placed in pans outside of latrines, sleeping tents	Individuals, Field Sanitation Teams, Certified Applicators
			Azamethiphos 1% (OP) Crystals		
	Pest Strip	Attract and kill mosquitoes	Dichlorvos 20% (OP) Pest Strip	Hung in sleeping tents, working areas, dumpsters	
Field Use Pesticides	Sprayed Liquids (emulsifiable concentrates, ECs)	Kill flies, mosquitoes, crawling insects	Chlorpyrifos 45% (OP) Liquid	Sprayed in corners, cracks, crevices	Field Sanitation Teams or Certified Applicators
			Diazinon 48% (OP) Liquid	Sprayed in corners, cracks, crevices	Certified Applicators
			Malathion 57% (OP) Liquid		
			Propoxur 14.7% (C) Liquid		
	Sprayed Powder (wettable powder, WP)	Kill flies, mosquitoes, crawling insects	Bendiocarb 76% (C) Solid		
	Fogs (Ultra-Low Volume Fogs, ULVs)	Kill flies, mosquitoes	Chlorpyrifos 19% (OP) Liquid	Large area fogging	Certified Applicators
			Malathion 91% (OP) Liquid		
Delousing Pesticide	Delousing Pesticide	Kill lice	Lindane 1% (OC) Powder	Dusted on EPWs, also available for personal use	Certified Applicators, Military Police, Medical Personnel

Figure 3. Active ingredients in pesticides of potential concern.

Active ingredients contained in pesticides of potential concern

Repellents	Pyrethroids	Organophosphates	Carbamates	Organochlorines
DEET	Permethrin	Azamethiphos	Methomyl	Lindane
	D-Phenothrin	Chlorpyrifos	Propoxur	
		Diazinon	Bendiocarb	
		Dichlorvos		
		Malathion		

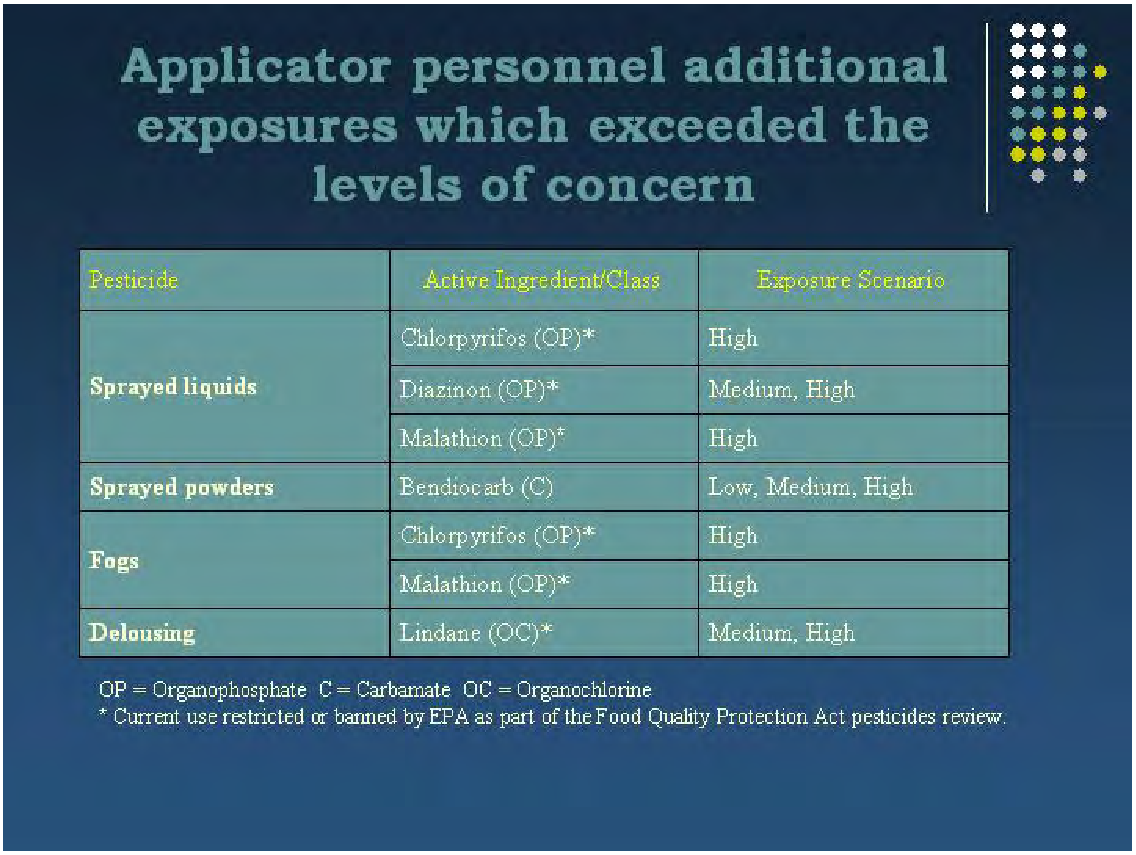
Figure 4. General military exposure levels reaching levels of concern

General Military population exposures which exceeded the levels of concern

Pesticide Type	Affected Group	Active Ingredient/Class	Exposure Scenario
Fly baits	Only individuals who handled (applied) fly baits	Azamethiphos (OP) *	Medium, High
		Methomyl (C)	High
Pest strips	General military population	Dichlorvos (OP)	Low, Medium, High
Sprayed Liquids	General military population	Chlorpyrifos (OP) *	High
		Diazinon (OP)*	High
		Malathion (OP)*	High
Sprayed Powders	General military population	Bendiocarb (C) *	Medium, High

OP = Organophosphate C = Carbamate
* Current use restricted or banned by EPA as part of the Food Quality Protection Act pesticides review.

Figure 5. Applicator exposure levels reaching levels of concern



Applicator personnel additional exposures which exceeded the levels of concern

Pesticide	Active Ingredient/Class	Exposure Scenario
Sprayed liquids	Chlorpyrifos (OP)*	High
	Diazinon (OP)*	Medium, High
	Malathion (OP)*	High
Sprayed powders	Bendiocarb (C)	Low, Medium, High
Fogs	Chlorpyrifos (OP)*	High
	Malathion (OP)*	High
Delousing	Lindane (OC)*	Medium, High

OP = Organophosphate C = Carbamate OC = Organochlorine
* Current use restricted or banned by EPA as part of the Food Quality Protection Act pesticides review.

Guidelines for pesticide and PB exposure are presented in the tables 2 and 3 and were used to classify participants into high and low exposure categories based on prior OSAGWI interviews and current interviews.

Table 2. Guidelines for Pesticides

Low exposure

An individual is assigned to the low-exposure category for pesticides if he or she does not fit the guidelines for high exposure, as described below. For example, an individual exposed to pyrethroids other than via fogs, but no other pesticides, would be assigned to a low pesticide exposure group.

High exposure

An individual is assigned to the high-exposure category for pesticides if any of the following apply:

1) PCI reported experiencing acute signs and/or symptoms of pesticide overexposure, other than minor skin irritation, at least once. A general statement, such as "became ill" will qualify.

2) PCI probably applied pesticides from any of the following groups on two or more occasions: organophosphate (OP) emulsifiable concentrate (EC) or ultra low volume (ULV) products, carbamate ECs or powders, lindane used for enemy prisoners of war (EPWs), fly baits ($\geq$2 pounds handled), and/or fogs. PCI may or may not have worn adequate personal protective equipment (PPE).

3) PCI was probably present during applications of OP ECs/ULVs, carbamate ECs/powders, DDT, and/or fogs on two or more occasions.

4) PCI probably spent at least 1 week living/working in structures treated inside with OP and/or carbamate ECs, ULVs, powders, DDT, and/or pest strips, and likely experienced substantial post-application exposure.

5) PCI probably applied DEET to self at least 30 times. PCI must provide enough information to conclude that usage was equivalent to or above this level. DEET application 30 times per month is the 25th percentile value determined by the RAND (2000) survey for ground forces who used DEET (50% reported no use).

Table 3. Guidelines for PB

Low exposure

An individual is assigned to the low-exposure category for PB if no acute signs and/or symptoms of exposure were reported *and* any of the following apply:

1) The individual reported not using PB.

2) The total dose reported was less than or equal to 180 mg PB active ingredient.

3) The individual reported using PB, but could not recall sufficient details to conclude that the dose was probably greater than 180 mg PB active ingredient.

High exposure

Individuals are assigned to the high-exposure category for PB if either of the following apply:

1) The total dose was probably greater than 180 mg PB active ingredient.

2) The individual reported taking any PB and also reported experiencing acute signs and/or symptoms of exposure.

PB and pesticide exposure were categorized as high and low based on the previous OSAGWI interviews, the current SRBI interviews and with the current exposure interviews with study staff. From these interviews, 117 PCIs were categorized in the high pesticide exposure group and 43 were categorized in the low pesticide exposure group. Eighty-five PCIs were categorized in the high PB group and 75 were categorized in the low PB group. Additional categorization for pesticide and PB exposure and Khamisiyah notification (identifying those potentially exposed to chemical weapons) are listed in Table 4.

Table 4. PB and Pesticide Exposure Categories

Self-Reported PB Exposure during the Gulf War		
	Frequency	**Percent**
Yes	**118**	**74**
No	**33**	**20**
Don't Know	**9**	**6**
Total	**160**	**100**
Self-Reported Pesticide Exposure during the Gulf War		
	Frequency	**Percent**
Yes	**122**	**76**
No	**30**	**19**
Don't Know	**8**	**5**
Total	**160**	**100**
Exposure Categories for PB and Pesticides		
	PB	**Pesticides**
Low	**75**	**43**
High	**85**	**117**
Total	**160**	**160**
Khamisiyah Weapons Depot Notification		
	Frequency	**Percent**
Yes	**59**	**37**
No	**101**	**63**
Total	**160**	**100**

Task 1d. Identify pool of potential subjects for each of four exposure categories to recruit

Combining the previously described high and low exposure groups for the pesticide and PB groups allowed for four category groupings (Table 5). The categories include high pesticide and high PB exposure, high pesticide and low PB, low pesticide and high PB, and low pesticide and low PB. The goal of the study was to recruit 40 study participants from each of the four exposure categories with the study participants sequentially assigned to one of the four study groups based on exposure combination. However, the low pesticide/low PB (n =25) and the low pesticide/high PB (n = 18) groups were smaller than expectation and did not allow for such large groupings (Table 5).

Table 5. Four Exposure Categories for PB and Pesticides

	Pesticide categories		
PB categories	**Low**	**High**	**Total**
Low	**25**	**50**	**75**
High	**18**	**67**	**85**
Total	**43**	**117**	**160**

Task 1e. Screen potential subjects for exclusion criteria

The exclusion criteria for this study included current substance abuse, and/or substantial traumatic brain injury or other documented neurological illness precluding the use of a computer. Prior substance abuse and current medications were recorded but did not constitute exclusion criteria. These exclusion criteria were chosen so that study participants who may perform poorly on cognitive testing for known reasons other than environmental exposures could be screened out to prevent potential study confounders.

From the SRBI telephone interviews, a review of reported health symptoms was performed and no participant from these interviews reported significant head injury or other significant neurological illness that might interfere with performing the cognitive and computer testing parts of the study protocol. There was one case who reported a history of an acoustic neuroma recently removed, one case of a non-malignant meningioma removed with complete recovery, one case of multiple sclerosis (MS) and two cases of mini-stroke or transient ischemic attack (TIA). However, all of these study participants were able to complete the entire study protocol. In the 28 recruitment trips conducted, none of the study participants was screened out based on these criteria.

Subject recruitment has been completed. PCIs consenting to participate were asked questions to determine whether they met preliminary inclusion criteria for the study (that is, that they participated in the OSAGWI interviews (1997-1998), were not currently in treatment for substance abuse, did not have sensory or motor impairments precluding use of the computer, and did not sustain a serious brain injury. Screening for exclusion criteria occurred during the telephone recruitment phase of the study and was ongoing during the study recruitment efforts.

Task 2a. Recruitment of 160 study subjects and arrange for travel to multiple study sites.

Forty participants were recruited during year 4 and completed the study protocol (cognitive evaluation, psychological interviews and exposure questionnaires). This group included 32 men and 8 women; 6 participants were active duty personnel and 34 were veterans. Combined with the recruitment totals for years 1, 2, & 3 (12, 47, and 60, respectively), a total of 159 study participants was recruited. Subject recruitment efforts are presented in the table below. Fifteen additional potential subjects were interested in participating in the study but either had scheduling conflicts during our recruitment trip to their area (n = 8), had recently moved to another state (n=3), had a family emergency and cancelled their appointment with us (n = 1), or cancelled for no stated reason (n = 3).

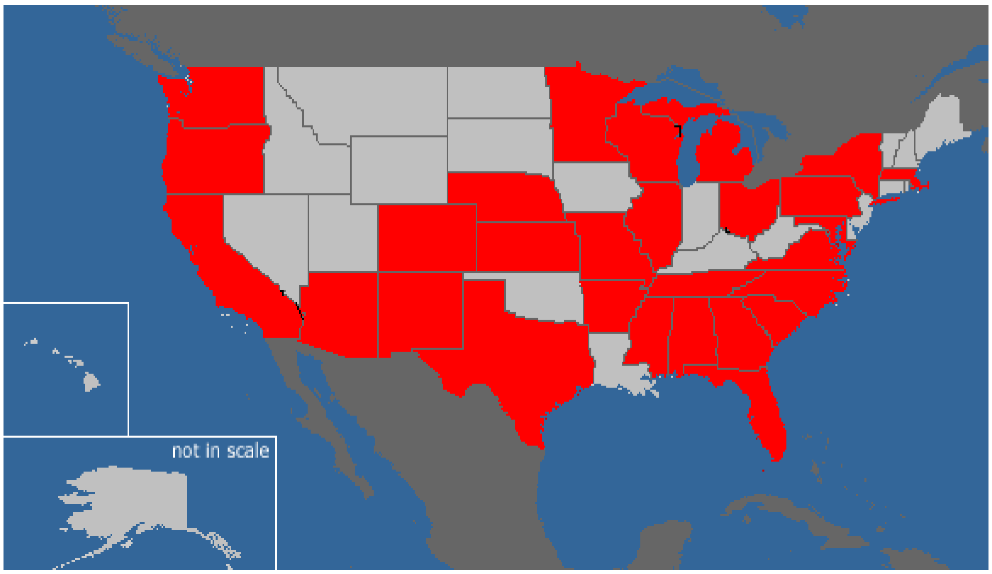
Table 6. Subject Recruitment Efforts for Years 1 -4

Study Year	**Frequency**	**Projected**	**Percent**
Year 1	12	20	60%
Year 2	47	50	94%
Year 3	60	50	120%
Year 4	40	40	100%
Total recruitment	159	160	99%

During years 1-4, recruitment trips were conducted in Texas, Alabama, California, Tennessee, New Mexico, Arkansas, Missouri, Illinois, Ohio, Pennsylvania, Maryland, New York, Florida, Georgia, Oregon, Nebraska, Mississippi, North Carolina, South Carolina, Michigan, Wisconsin, Minnesota, Washington, Virginia, New Mexico, Colorado, Kansas and

Arizona. In total, 160 study subjects were originally projected to be recruited for Years 1-4, and a 99 percent recruitment rate was achieved for total study recruitment with only four individuals declining to participate. These recruitment trips were successful with only four cancellations of scheduled participants. This resulted in recruitment trips to 28 states. See figure 2 below for a map of states visited for total recruitment efforts.

Figure 2. Recruitment trips for years 1- 4



Although the current address for each PCI was obtained by SRBI during their telephone interviews, we have found that many of the PCIs are quite mobile and have moved to different states from their previous SRBI interview residence. However, using internet and telephone searches and interagency agreements for address searches, we were able to find correct addresses for most of the potential study participants. In addition, one active duty personnel had been deployed overseas and was subsequently not able to participate during year 4 of the study. We were however able to recruit 6 additional active duty personnel to participate in the study during year 4 for a total of 14 active duty study participants. The exposure classifications are presented below and include 117 high pesticide, 42 low pesticide, and 85 high PB, 74 low PB categories.

Table 7. Exposure Classifications for 159 Study Participants			
PB categories	**Pesticide Categories**		
	Low	**High**	**Total**
Low	24	50	74
High	18	67	85
Total	42	117	159

Table 8. PCI Current Residence by State

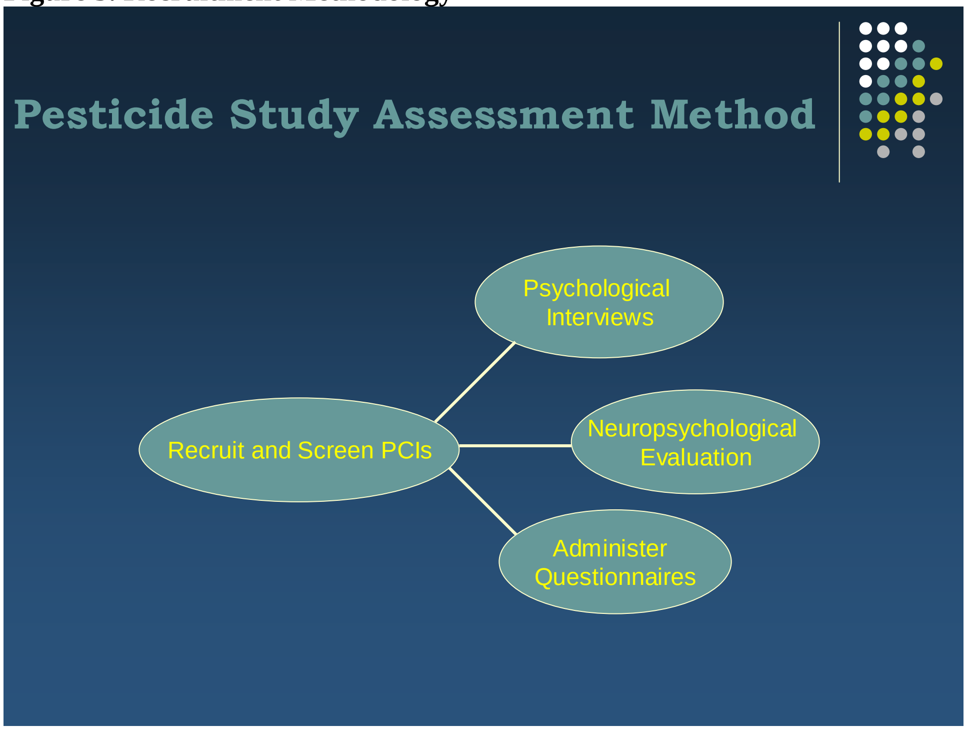
AL	4	MS	3
AR	7	MT	1
AZ	4	NC	15
CA	8	NE	4
CO	7	NH	1
CT	1	NJ	1
DC	1	NM	5
FL	23	NV	2
GA	14	NY	5
HI	1	OH	2
IA	1	OK	3
IL	4	OR	1
IN	3	PA	12
KS	4	SC	3
KY	2	TN	17
LA	1	TX	27
MA	1	UT	1
MD	11	VA	12
ME	1	WA	14
MI	8	WI	10
MN	1	Deployed	7
MO	22		

Recruitment Methodology

When recruiting study participants, the PI or study staff contacted PCIs participating in the SRBI interviews and described the study and established whether the PCI would participate in the cognitive evaluation. The initial contact with the study staff consisted of a description of the study, the types of assessment used, time required, and reimbursement for their time and effort. Subjects had an opportunity to ask questions about the procedure. They were informed that whether or not they participate had no bearing on their medical care and that, if they chose to participate, they could withdraw at any time without prejudice. They were asked to indicate whether they wished to participate, wished not to participate, or wished to defer this decision. In the latter case they were asked whether we may contact them again to determine their decision.

Gulf War veterans currently on active duty were contacted at home in the evening hours and were not contacted during duty hours. Active duty PCIs were not compensated for their participation as there are restrictions on compensation to active duty personnel. PCIs consenting to participate were asked questions to determine whether they met preliminary inclusion criteria for the study (that is, that they participated in the OSAGWI interviews (1997-1998), were not currently in treatment for alcohol or other substance abuse, did not have sensory or motor impairments precluding use of the computer, and did not sustain serious brain injury). Prior substance abuse and current medications were recorded but did not constitute exclusion criteria. An appointment during one of the field trips was scheduled for subjects agreeing to participate. PCI veterans retained in the study sample were presented the study consent form for signature. The study methodology is presented in Figure 5.

Figure 5. Recruitment Methodology



Task 2b. Perform cognitive evaluations and psychodiagnostic interviews with 160 participants

The goal for years 1- 4 was to recruit and perform cognitive and psychodiagnostic interviews with 160 study participants. As described above, a total of 159 study participants was recruited in years 1-4 (99% recruitment rate). In addition, all 159 of the study participants completed the entire study protocol and did not express any difficulties with the length of the examination. The cognitive evaluations were completed in 1.5 hours for most of the study participants and the psychodiagnostic interviews required an additional twenty minutes in most cases to complete. Study participants were able to take breaks during the study protocol session if they felt they needed them and could have filled out their questionnaires and mailed them back if necessary. With this strategy, there was little missing data from the study protocols. However, when encountering missing data during data analysis, interpretative statistics were employed whenever possible.

A description of the neuropsychological domains and the complete neuropsychological test battery are presented in tables 9 and 10 followed by a description of the study instruments and procedures.

Table 9. Definitions of Neuropsychological Domains

I. General Intelligence: IQ scores in all domains or in a specific domain (verbal or visual-motor); academic skills; performance on tests of reading, spelling, arithmetic, vocabulary, academic knowledge.
II. Attention, Executive System: Capacity to focus on incoming stimuli; includes vigilance, tracking and capacity to divide attention between competing stimuli.
III. Motor: Speed and dexterity in completing manual dexterity tasks.
IV. Visuospatial function: Processing of nonverbal information such as visual designs, visual constructions, and geographic information; includes sequencing, organization (mental) and constructional ability.
V. Memory: Anterograde memory function involves encoding, storing, retrieving and retaining new information. Retrograde memory function refers to ability to recall information learned in the past.
VI. Mood/Personality: Includes temporary and characterologic mood states and characterologic personality traits or tendencies.
VII. Motivation and Malingering: An evaluation of effort.

Table 10. Full Neuropsychological Test Battery.

TEST NAME	DESCRIPTION	OUTCOME MEASURE
I. Tests of Premorbid Functioning		
Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997) Information subtest	Information usually learned in school; to assess native intellectual abilities	Raw Score
Boston Naming Test (BNT; Kaplan et al., 1983)	Confrontation naming of line drawings; to assess verbal abilities	Raw Score
II. Tests of Attention, Vigilance and tracking		
Trail-making Test (Reitan &Wolfson, 1985)	Timed connect-a-dot task to assess attention and motor control requiring sequencing (A) and alternating sequences (B)	Time to Completion
Computerized Continuous Performance Test (CPT; Letz & Baker, 1988)	Target letter embedded in series of distractors; to assess sustained attention and reaction time	Reaction Time Total Errors
Wisconsin Card Sorting Test (WCST; Heaton et al, 1993)	Requires use of feedback to infer decision making rules; assesses problem solving ability and flexibility	Total # Sorts
III. Tests of Motor Function		
Finger Tapping Test (FTT; Letz and Baker, 1988)	Speed of tapping with index finger of each hand; assesses simple motor speed	Mean Taps
Grooved Pegboard Test (Klove, 1963)	Speed of inserting pegs into slots using each hand separately; assesses motor coordination and speed	Time to Completion
IV. Tests of Visuospatial Function		
Hooper Visual Organization Test (HVOT; Hooper, 1958)	Identifying objects from line drawings of disassembled parts; assesses ability to synthesize visual stimuli	Raw Score
Rey-Osterreith Complex Figure (ROCFT; Corwin & Blysma, 1993)	Copying a complex geometric design; assess ability to organize and construct	Raw Score

TEST NAME	DESCRIPTION	OUTCOME MEASURE
V. Tests of Memory		
California Verbal Learning Test (CVLT II; Delis et al., 1987)	List of 16 nouns from 4 categories presented over multiple learning trials with recall after interference; assesses memory and learning strategies	Total Trials 1-5 Long Delay Total
ROCFT-Immediate and 20 minute recall	Immediate and Delayed recall of a Complex figure	Raw Score
Stanford-Binet Copying Test (Terman & Merrill, 1973)	Immediate and 10 minute delay of 16 designs	Raw Score
VI. Tests of Personality and Mood		
Profile of Mood States (POMS; McNair et al., 1971)	65 single-word descriptors of affective symptoms endorsed for degree of severity and summed on six mood scales	T-Scores
VII. Tests of Motivation		
Test of Motivation and Malingering (TOMM; Tombaugh, 1996)	Immediate forced choice recognition of line drawings of 50 common objects; assesses motivation and malingering	Raw Score

Assessment Instruments and Procedures

1. Cognitive Assessment.

A tester who was blind to the exposure status of the subject administered the neuropsychological test battery. The neuropsychological test battery assessed the functional domains of general intelligence, attention, executive abilities, motor function, visuospatial skills, memory, and mood (Table 9). The battery is described in detail in Table 10. It included 1) tests designed to tap relatively stable native intellectual abilities including the Information Subtest from the WAIS-III, and the Boston Naming Test. On these tests, it was expected that the scores would be consistent with estimated native IQ based on age, education, and occupational history. And, 2) tests shown to have high specificity and sensitivity for detecting changes in neuropsychological functions that have demonstrated utility in the assessment of toxicant-induced brain damage and psychiatric disorders in past studies. The domains included in this category are attention, executive function, visuospatial abilities, psychomotor skills, mood, and memory.

Sustained attention was defined as the number of errors on a test of continuous performance (CPT). The CPT is a computer-assisted test from the Neurobehavioral Evaluation System (NES), an instrument widely used in the field of occupational health. NES is an adaptation of traditional neuropsychological instruments that computerizes stimulus presentation and recording of responses. The NES tasks have reliable psychometric properties and demonstrated validity in epidemiological and laboratory studies of exposure to a wide variety of neurotoxicants. Also used as measures of executive functioning were measures of cognitive flexibility (Wisconsin Card Sort test) and alternation of set (Trail Making Test, part B).

Motor functioning was measured by the mean of five trials on each hand on the finger tap test, the latency of response on the finger tap test and the time to completion on the grooved pegboard test. Although not generally considered a test of motor functioning, mean reaction time on the CPT test was used as a measure of information processing speed in this battery.

Previous studies of occupational pesticide exposure have documented changes in information processing speed and motor reactions (NCTB). Therefore, we predicted decreased CPT reaction time performance in the high-exposed PCI group and motor slowing on the additional measures.

The test battery also included the Profile of Mood states as a self-report assessment of current mood. The indicators of importance are current fatigue, confusion, tension and depression. Mood has been shown to be associated with changes in subcortical-limbic system and neurotransmitters as a result of toxicant exposures including pesticides (Bazylewicz-Walcczak et al., 1999; Stephens et al., 1995; Steenland et al., 1994) and as such, mood was treated as an outcome measure rather than as strictly a potential confounding variable.

In order to assess visuospatial processing, we administered the Rey-Osterrieth Complex Figure Test and documented total scores for the copying subtest using a standardized scoring system (Rey-Osterrieth scoring out of 36). In addition, a qualitative scoring system was also used to assess approach to the task and specific types of errors committed. We expected that individuals with increased exposures would have difficulty maintaining the overall configuration, tremulous writing and segmentation as a result of basal ganglia dysfunction commonly seen in these types of exposures. In addition, the Stanford-Binet copying task was used in this test battery to document impairment in visuoconstruction as has been found in our prior research. The total score for copying (out of 16 possible) was expected to be diminished in those who had significant neurotoxicant exposures. In addition, we also compared total number of errors (out of 120 possible) as well as type of errors as discussed above.

Individuals who have documented exposures to neurotoxicants have shown difficulty in the areas of acquisition and retrieval on tests of short-term memory. Therefore, we examined verbal and nonverbal memory with the use of the Rey-Osterrieth Complex Figure Immediate and Delayed recall and the California Verbal Learning Test (CVLT-II) measures of total recall trials 1 to 5 (raw score) and Long-delay free recall (raw Score).

Lastly, a measure of response consistency was used to document the possibility of diminishment in motivation. Raw scores (out of a possible score of 50) were computed; few individuals were expected to fall below a score of 45 (indicating decreased motivation).
In the event of decreased motivation scores on this test, analyses were performed with and without these individual's test scores to assess for potential differences. If there were significant differences between the groups, then the group with low motivational scores were removed from the dataset.

Because this study examines neuropsychological functioning in pesticide-exposed individuals many years after their GW exposures, how does one decide if decreased performance in cognitive functioning is actually associated with pesticide exposure or if those individuals with cognitive deficits simply report more pesticide exposure? One way to examine this problem is to compare patterns of cognitive performance in relation to the reported exposure.

Epidemiological studies during the past 30 years have examined the impact of exposure to metals (e.g., lead, mercury, arsenic), organic solvents (e.g., trichloroethylene, n-hexane, petroleum distillates), and pesticides (e.g., organophosphates, carbamates) on brain functioning and found different cognitive patterns with these exposures. For example, studies of solvent exposure have reliably shown disturbances in executive function, attention, visuospatial skills, short-term memory, and mood (Anger, 1990, White et al., 1992 and Echeverria & White, 1992). Studies of lead-exposed workers have yielded similar findings along with decrements in verbal reasoning and motor functions (Baker et al., 1984, Hanninen et al., 1978 and Yokoyama et al., 1988). Studies of pesticide-exposed agricultural workers have shown disturbances in information processing speed and mood and sequelae from overt poisoning from organophosphate pesticides can result in lasting deficits in the domains of visuomotor, attention/executive functioning, motor functioning and mood. Therefore, we examined both specific test performance and the pattern of cognitive performance in the

domains of attention/executive functioning, memory, visuospatial skills, motor skills and mood and controlled for other factors (e.g., age, education, gender, prior exposures, alcohol abuse, and psychiatric diagnoses including post-traumatic stress disorder) likely to influence performance on the cognitive tests (Grasso et al., 1984, Hanninen, 1988, Proctor et al, 1996 and Letz, 1993) when significantly different between the groups.

2. Psychological Assessment.

Subjects were administered the Structured Clinical Interview for DSM-IV (SCID) and a current Global Assessment of Functioning score was assessed. This instrument has demonstrated reliable psychometric properties for determining the presence or absence of current or past major Axis I disorders. Dr. Krengel, who administered the CAPS, was blind to the exposure data when administering the Clinician Administered PTSD Scale IV (CAPS), a state-of-the-art instrument for confirming the diagnosis of current or past PTSD and for evaluating the intensity, frequency, and severity of the disorder and its individual symptom criteria. Extensive research now indicates that this instrument has highly acceptable psychometric properties. Subjects filled out a series of self-report, paper and pencil measures designed to confirm and define symptoms of PTSD (PTSD Checklist), and to identify traumatic events, military or civilian (Modified Life Events Checklist, Traumatic Events) (Table 11).

Dr. Krengel also conducted a semi-structured clinical interview eliciting information pertaining to recent past and current mood disorders, substance use, neurological and medical illness, traumatic brain injury, and history of other traumatic events. Subjects were asked questions specifically related to recent occupational history (including possible occupational exposure to neurotoxicants), family history of psychiatric disorder, and life stressors.

Treatment of Data

The aims of this study were to determine the cognitive and neurological effects of pesticide exposure in specific groups of GW veterans, to determine the cognitive and neurological effects of PB exposure in specific groups of pesticide exposed GW veterans, and to assess for interaction effects in GW veterans with multiple chemical exposures (PB, pesticides, low-level nerve agents).

We examined the relationship between neurotoxicant exposure and neuropsychological performance through multivariate multiple regression and multivariate analysis of variance. This included using indicator variables to account for group status (1 = Low PB, Low Pesticide, 2 = High Pesticide, low PB, 3 = Low Pesticide, High PB, 4 = High Pesticide, High PB) as well as individual risk factors and intervening risk factors that might be related to outcomes. Additional analyses exploring the interactions between the exposures and neuropsychological outcome were pursued. We looked at the relationship of stress and health symptoms through the multiple regression analyses and MANOVA as described above. Steps were employed to minimize missing data including offering breaks during cognitive testing, allowing participants to complete questionnaires at home and mailing them back and completing psychological interviews by telephone (when necessary due to time constraints or fatigue of study participants). However when data was not obtainable, the missing data was interpolated statistically whenever possible by comparing means of similarly answered questions.

Task 2c. Obtain information about current health status, environmental and occupational exposures, medical or psychological treatments, and any recent medical or psychiatric diagnoses for 159 study subjects by study questionnaires.

All 159 study participants recruited in years 1-4 completed the study questionnaire, which was comprised of several health and mental health scales. These include: the health symptom checklist, Brief Symptom Inventory (BSI), PTSD checklist (PCL), Modified Life Events Checklist (Traumatic events), Veterans Version of the SF12 (SF12V), and the pesticide exposure questionnaire (SRBI questionnaire). See Table 11 for questionnaire descriptions and Table 12 for frequencies of psychiatric diagnoses, medical conditions and health symptom reports for the 159 study participants. In general, psychiatric diagnoses were highly consistent with rates from our prior studies of GW veterans for PTSD (8.8%) and depression (10.1%) when measured by a structured clinical interview (Sullivan et al., 2003). The most common medical diagnoses reported in the study sample included allergies, hypertension, arthritis, deafness, asthma, cancer, neurological diseases and irritable bowel syndrome. In depth health symptom questions from the 34-item health symptom checklist (HSC) in the study questionnaire (see Table 11) showed elevated rates of joint pain (67%), sleep difficulties (59%), muscle pain (51%), forgetfulness (47%), concentrating difficulties (43%), body tingling (42%), word finding problems (38%) and weakness (35%). These same health symptoms were the most commonly reported in our prior studies and clinical evaluations of treatment-seeking Gulf War veterans from the New England area, with the exception of weakness and body tingling (Proctor et al., 1998; Sullivan et al., 2003). When comparing health symptoms and medical diagnoses by pesticide exposure, all diagnoses were higher in the high pesticide exposed group (diabetes 12 vs. 3; heart attack 3 vs. 0; arthritis 26 vs. 7, lung disease 8 vs. 1, chronic rash 31 vs. 6; high blood pressure 42 vs. 11) but no statistically significant differences were found. Analysis on individual pesticides of Potential concern (POPCs) were more information in terms of individual health symptoms and exposures (see section 3b).

Table 11. Study Questionnaire Descriptions

Name	Description
Demographics	Subjects report information on age, education, gender, ethnicity, marital status, GW duty service (active vs. reserve/National Guard), military rank and current military status.
SF12V	Veterans version of the SF12 which compares functional health-related quality of life. It includes a physical component score and a mental component score.
Health Symptom Checklist (HSC)	A comprehensive list of 34 frequently reported health and mental health symptoms. The HSC determines how often in the past 30 days the health symptoms were experienced. Symptoms from nine body systems are assessed (cardiac, pulmonary, dermatological, gastrointestinal, genitourinary, musculoskeletal, neurological, and psychological).
Medical Conditions	Included in this checklist is a list of 21 medical conditions that the subject is asked to rate if they have ever had the condition, how it was diagnosed (self or doctor) and when it was diagnosed.
Brief Symptom Inventory (BSI)	The Global Severity index of the BSI is a summary index that represents the most sensitive single inventory indicator of a subjects' psychological distress level by combining information on a number of psychological symptoms and their intensity.
PTSD checklist (PCL)	A 17-item checklist following DSMIII-R or DSM-IV guidelines and is a structured interview for clinical diagnosis of PTSD.
Modified Life events checklist (Traumatic Events)	Modified version of the life events checklist to check for traumatic life events.
Structural Neurotoxicant Assessment Checklist (SNAC)	The SNAC assesses the degree of past exposure to neurotoxicants during civilian and military occupations includes questions pertaining to recent occupational and environmental exposures. Questions include length stay, geographical location, and environmental exposure during deployment (type, intensity, frequency, duration, locale).
Pesticide Exposure Questionnaire (SRBI brief questionnaire)	This telephone interview was conducted by SRBI to obtain pesticide and PB exposure estimates. Questions include what pesticides were used during the Gulf War and what most pressing health problems that the respondent currently reports.
Telephone Recruitment form	This telephone recruitment form is used by study staff to recruit and track responses for potential study participants. Questions include current medical diagnoses, medication use, and participation in other Gulf War related studies.

Table 12. Psychiatric Diagnosis and Health Symptom Report in 159 Participants		
Interview Diagnosis	**Frequency**	**Percent**
PTSD	14	8.8
Major Depression	16	10.1
Multiple Chemical Sensitivity	2	1.3
Chronic Fatigue Syndrome	4	2.5
Medical Conditions	**Frequency**	**Percent**
Hypertension	54	34*
Asthma	18	11*
Heart Attack	3	2
Diabetes	15	9
Multiple Sclerosis	1	1
Other Neurological Disease	12	8
Cancer	18	11
Mini Stroke / Cerebrovascular Disease	4	3
Allergies	49	31*
Arthritis	43	27
Irritable Bowel Syndrome	11	7
Thyroid disorder	8	5
Tumors or growths	3	2
Neuropathy	4	3
Lung Disease	13	8
Deafness	23	15

Health Symptoms	Frequency	Percent
Joint Pain	107	67
Skin Rash	34	21
Sleep Trouble	94	59
Diarrhea	32	20
Upset stomach	40	27
Difficulty Concentrating	69	43
Confusion	30	19
Forgetfulness	75	47
Muscle pain	81	51
Weakness	55	35
Body Tingling	66	42
Word Finding Problems	61	38

*** symptoms higher than would be expected for general population for same age based on the National Health Interview Survey of CDC (2006) http://www.cdc.gov/asthma/nhis/06/table4-1.htm and the National Health and Nutrition Examination Study (NHANES, 2004) http://www.hypertensiononline.org/slides2/slide01.cfm?q=national+health+and+nutrition+examination+survey&dpg=8 .**

Task 3a. Data entry of all questionnaires and evaluations and quality control measures have been completed.

Interview findings, neuropsychological assessment results, and questionnaire data for each of the 159 completed study participants were scanned into a dataset by using Teleform software and cleaned through quality control measures. SPSS datasets were created to analyze the data obtained. This procedure was ongoing as subject recruitment continued.

Task 3b. Statistical analyses of data obtained from cognitive evaluations and questionnaire data will be completed.

Multivariate analysis of variance of the complete 159 subject sample was computed to compare high and low pesticide exposures on neuropsychological measures, including the domains of attention/executive system, language, psychomotor, visuospatial and memory. The results are presented in Table 14. Overall, the results showed lowered mean test scores in the high pesticide exposed groups compared with the low pesticide exposed group on all domains of interest. However, few statistically significant differences between the exposure groups were found. Further breakdown of the exposure categories into pesticide x PB groups provided more sensitivity and are presented below.

When health symptom patterns were compared in a separate analysis using chi-square analyses, PCIs with high pesticide exposure reported significantly more difficulties with gastrointestinal difficulties, skin rash, muscle weakness, confusion and word-finding difficulties as measured by the 34-item Health Symptom Checklist (HSC) (Table 13). In addition, being in the high pesticide group was significantly associated with the musculoskeletal ($p=.03$) and mood and cognition ($p = .008$) subscales of the chronic multi-symptom illness criteria (CMI) of Fukuda (1998) and with total health symptoms reported on the HSC ($p=.01$). The Khamisiyah group was also significantly associated with the musculoskeletal ($p=.03$) and mood and cognition ($p = .03$) subscales of the CMI diagnosistic criteria (Fukuda et al., 1998). When comparing the four high and low pesticide x PB groupings, CMI diagnosis was significantly different in the high pesticide / high PB groupings ($p = .02$) as were the subscales of mood/cognition ($p = .003$) and fatigue ($p = .03$).

Other reported medical diagnoses were not significantly different in the high and low pesticide or PB groups. However, analysis comparing medical diagnoses among subjects with Khamisiyah notification (and potential low-level nerve agent exposure) showed significantly more irritable bowel syndrome in the notified group (20% of Khamisiyah group, $p= .005$,

odds ratio = 6.1). Regression analyses of the four groupings were performed as described in the treatment of data section. Results are presented below.

Table 13. Health Symptom Checklist Results in 159 Study Participants with PTSD included.

Health Symptom	Pesticide High Exposed % reporting n= 117	Pesticide Low Exposed % reporting n= 42	Chi-Square X^2 (p-value)	Odds Ratio OR
Diarrhea	25	5	.004	6.7
Upset Stomach	30	12	.02	3.2
Skin Rash	21	5	.002	7.9
Weakness	31	12	<.001	5.6
Muscle Pain	57	36	.02	2.4
Confusion	23	7	.02	3.9
Word Finding Difficulty	46	20	.003	3.4
Sleep Problems	68	36	<.001	3.8
Breathing trouble	20	2	.007	10.2
Body tingling	49	21	.002	3.5
General aches and pains	51	40	<.001	3.6
Twitching	34	17	.04	2.5
Forgetful	53	28	.006	2.8

*** Significant results presented (n = 34 total symptoms)**

Health Symptoms Checklist Results in 144 Study Participants without PTSD

Health Symptom	Pesticide High Exposed % reporting n= 103	Pesticide Low Exposed % reporting n= 41	Chi-Square X^2 (p-value)	Odds Ratio OR
Diarrhea	21	5	.02	5.1
Upset Stomach	30	12	.02	3.2
Skin Rash	25	5	.007	6.3
Weakness	37	10	.001	5.4
Muscle Pain	53	34	.05	2.1
Confusion	23	7	.02	3.9
Word Finding Difficulty	41	20	.02	2.8
Sleep Problems	64	34	.001	3.5
Breathing trouble	17	2	.02	8.0
Body tingling	46	20	.003	3.5
General aches and pains	69	39	.001	3.5
Twitching	34	17	.04	2.5
Forgetful	49	29	.03	2.3
Rapid heart rate	18	5	.04	4.4
Trouble concentrating	44	25	.04	2.4
Moody	42	24	.05	2.2

*** Significant results presented (n = 34 total symptoms)**

Table 14. Neuropsychological Outcomes in High and Low Pesticide Exposed Groups

Cognitive Domain	High Pesticide Group Mean (sd) N = 117	Low Pesticide Group Mean (sd) n = 42	Significance P-value
Attention/Executive			
Trails A – time to completion	31	29	.26
Trails B – time to completion	73	62	.40
WCST – number of sorts	3.6	3.9	.23
CPT – # false positives	1.6	2.4	.20
CPT - # no responses	.55	.19	.71
Psychomotor			
Finger Tap test – latency of response, preferred hand	177	170	.55
Finger Tap test – latency of response, non-preferred hand	191	182	.09
Finger Tap test - # taps preferred hand	52.4	54.0	.55
Finger Tap test - # taps non-preferred hand	52.2	53.6	.22
Grooved Pegboard - time preferred hand	74.9	73.5	.30
Grooved Pegboard – time non-preferred hand	79.7	76.9	.24
CPT – mean response time	398	381	.05
Visuospatial			
Hooper – total correct	26.5	26.2	.55
Stanford-Binet copy – total correct	4.9	5.2	.91
Rey-Osterrieth figure copy – total correct	27.1	27.7	.69
Memory			
CVLT – # correct trials 1-5	48.1	49.6	.31
CVLT – short delay # correct	10.1	10.3	.60
CVLT – long delay # correct	10.6	10.9	.59
CVLT – recognition # correct	14.4	15.1	.05
Rey- Osterrieth - immediate recall, # correct	16.5	17.7	.09
Rey-Osterrieth - delayed recall, # correct	15.5	16.9	.10
Stanford-Binet Recall - # correct	8.1	8.0	.65

Comparisons of PCIs with high pesticide exposure combined with high PB exposure (Group 4) performed worse than those with low PB exposures with lowered mean reaction times on the continuous performance test and mood functioning on the Profile of Mood States (POMS) when age, education, gender and PTSD were included as covariates. Visual memory was significantly different between the 4 exposure groups on the Rey-Osterrieth Complex figure test with Group 2 (high pest, low PB) showing the worst performance. In addition, health symptom reporting in high pesticide x High PB exposed groups was significantly associated with Chronic Multisymptom Illness (CMI) and specifically with the mood/cognition and fatigue subsets. There were no interaction effects found between the 4 exposure groups and Khamisiyah notification on the neuropsychological tasks.

Further analyses comparing pesticide x PB exposure groups are presented in Table 15. Multivariate analyses comparing the 4 pesticide x PB exposure groups (low/low; low/high, high/low; high/high) showed a significant main effect (p=.03) when comparing cognitive domains and significant differences between the motor (p =.01), mood (p=.03) and memory domains (p=.01) when age, education and gender were included as covariates and with the memory domain (p=.02) and the motor (p=.06) and mood (p=.06) domains when PTSD was added to the model as a covariate.

Table 15. Pesticide x PB Group Comparisons of Cognitive Domains

Pest x PB Group	Attention/Executive p-value =.16 Mean	Motor p = .01 Mean	Mood p = .03 Mean	Memory p = .01 Mean	Visuospatial p = .13 Mean	Language p = .66 Mean
Low/Low	168.0	1001.2	264.2	112.9	57.9	57.5
High/Low	173.3	1016.2	268.4	104.7	56.7	56.5
Low/High	148.7	983.1	253.5	123.9	60.8	57.2
High/High	165.6	1040.9	279.6	108.2	59.6	56.9

Pesticide x PB Group Comparisons with PTSD included in the model

Pest x PB Group	Attention/Executive p-value =.21 Mean	Motor p = .06 Mean	Mood p = .06 Mean	Memory p = .02 Mean	Visuospatial p = .09 Mean	Language p = .67 Mean
Low/Low	168.2	1003.8	264.0	110.9	57.2	57.4
High/Low	171.1	1013.1	267.0	105.7	56.7	56.5
Low/High	148.7	983.2	253.5	123.9	60.8	57.2
High/High	165.6	1040.9	279.6	109.7	59.6	57.0

Individual univariate analyses of variance were then conducted for the cognitive domains showing significant differences between the four exposure groups when controlling for age, education and gender. These analyses showed that Continuous Performance Test (CPT) mean reaction time (p=.006), Rey-Osterrieth Complex figure delay (p=.05) and immediate recall (p=.006), as well as the Profile of Mood States subscores of Tension (p=.02), Depression (p=.04) and Fatigue (p=.002) were significantly different between the four exposure groups with the high pesticide x high PB exposure group (Group 4) scoring significantly worse in the CPT test (p=.007) and the POMS tests and the high pesticide x low PB group (Group 2) scoring significantly worse on the immediate and delayed conditions of the Rey-Osterrieth Complex Figure test (see figures 6-8). These results were still significant

when PTSD was added to the model as a covariate (CPT p=.02, Rey -Osterrieth immediate recall p=.008, Rey-Osterrieth delayed recall p =.02) In addition, the CMI diagnosis was significantly different in the high pesticide x high PB group (p = .02) as well as the Fukuda (1998) subscales of mood/cognition (p = .003) and fatigue (p = .03).

Figure 6. Psychomotor results for Pesticide x PB groups

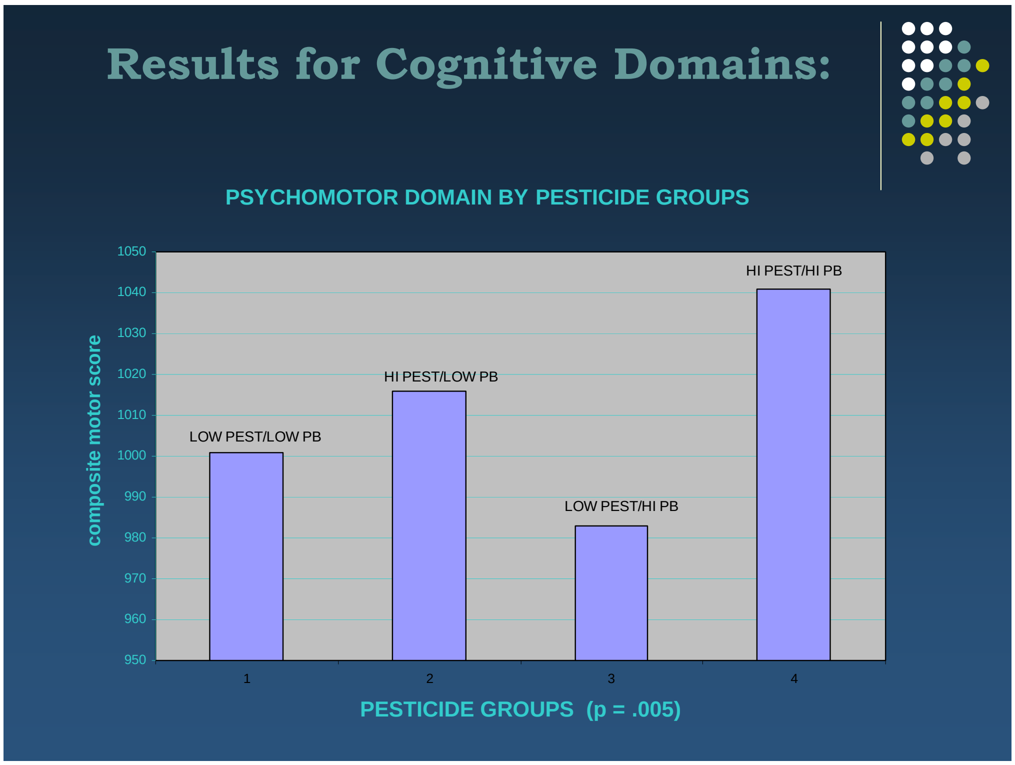


Figure 7. Memory results in Pesticide x PB groups

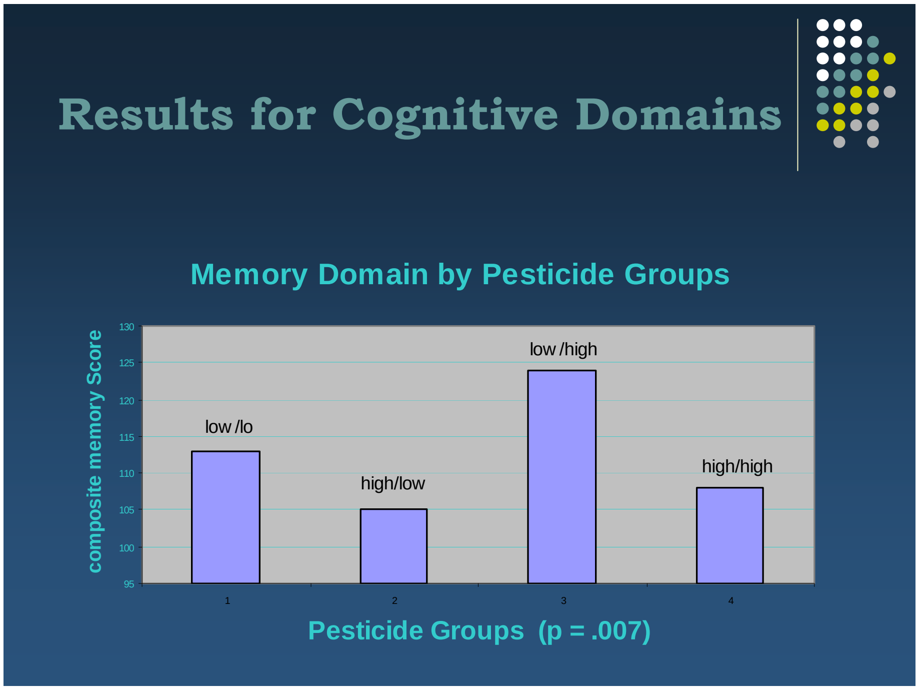
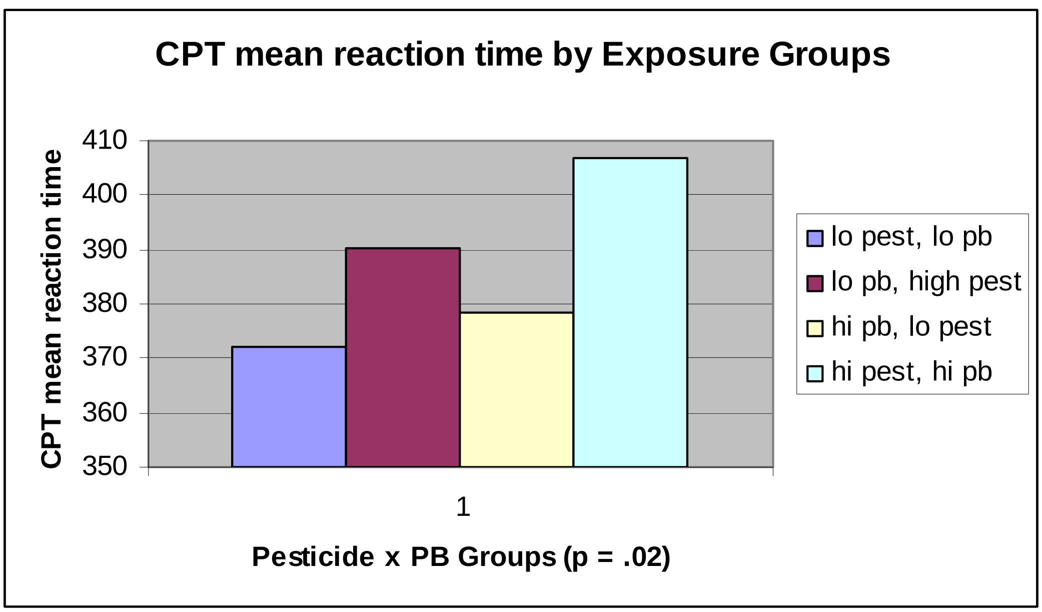
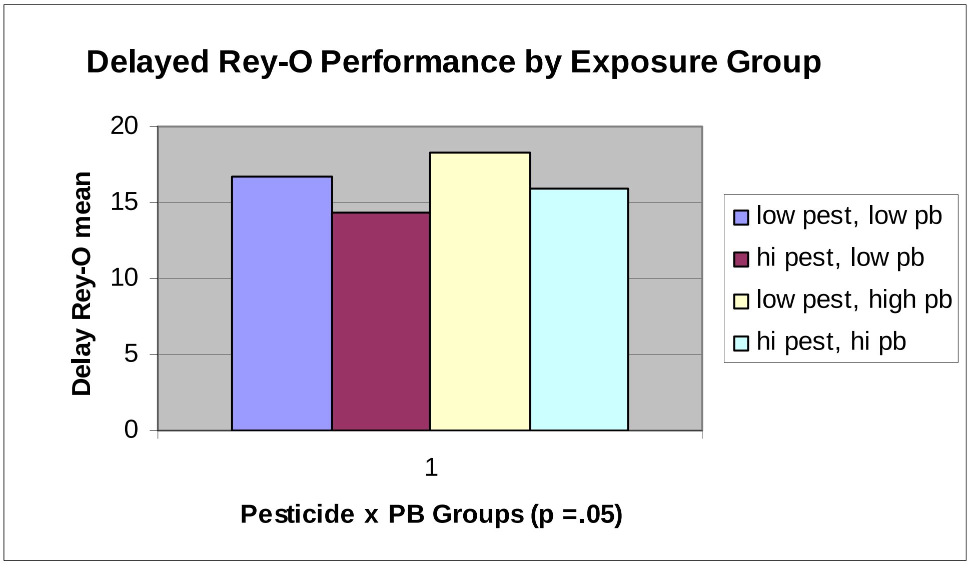


Figure 8. Continuous Performance Test by Pesticide Exposure Groups



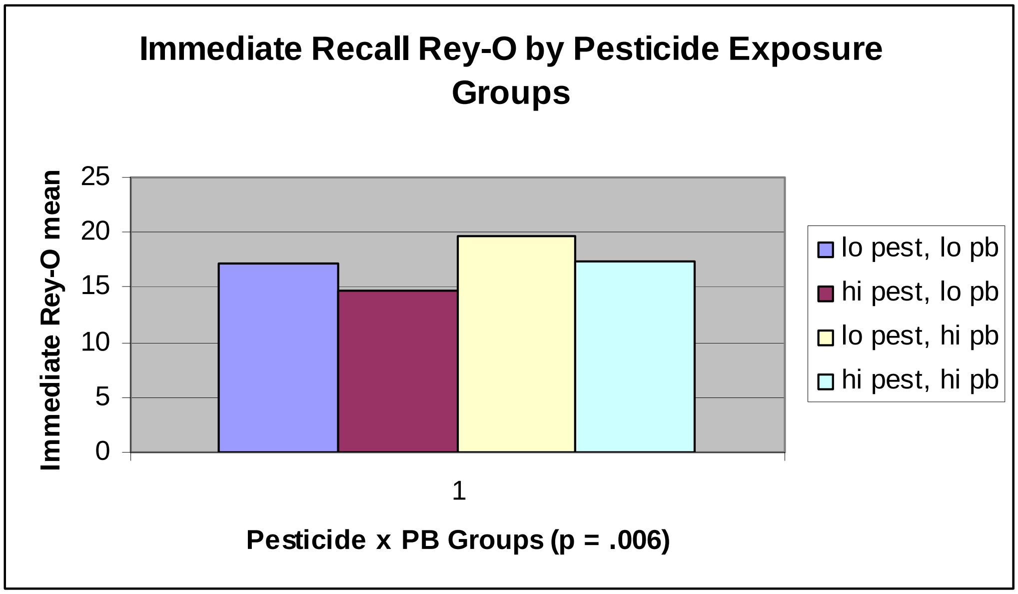
There was a significant main effect observed between the pesticide/PB groupings on the CPT reaction time measure and individual comparisons showed that there was a significant difference between exposure Group 1 (low/low) and Group 4 (high/high) at p=.007.

Figure 9. Delayed Rey-Osterrieth Performance by Pesticide Exposure Groups



There was a significant main effect among the 4 exposure groups for the delayed Rey-Osterrieth visual memory task and individual comparisons showed that there was a significant difference between exposure Group 2 and Group 3 and between Group 2 and Group 4. This finding suggests that the high pesticide/low PB group was the worst performing in terms of visual memory recall while the low pest/low PB and low pest/high PB group performed significantly better on this task.

Figure 10. Immediate Rey-Osterrieth Performance by Pesticide Exposure Groups

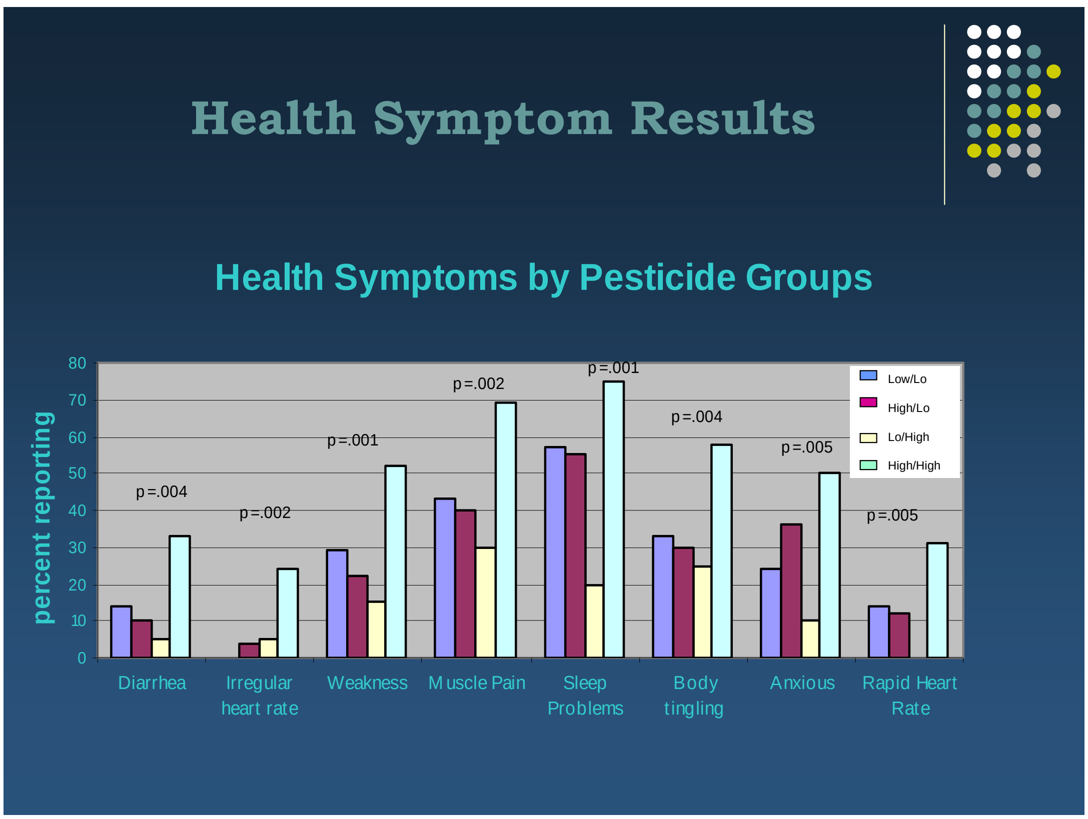


When health symptom patterns were compared in a separate analysis using chi-square analyses, PCIs in the high pesticide x high PB reported significantly more difficulties with joint stiffness, muscle pain and weakness, gastrointestinal difficulties, rapid and irregular heart rates, breathing trouble, sleep and fatigue difficulties, body tingling and twitching, anxiety and mental confusion than the other three exposure groups (high/low, low/high, low/low) as measured by the 34-item health symptom checklist (see table 16 below and figure 11).

Table 16. Health Symptom Results by Pesticide Groups

Health Symptom	Low Pesticide x Low PB % reporting n= 21	High Pest x Low PB % reporting n=50	Low Pest x High PB % reporting n=20	High Pest x High PB % reporting n= 68	Chi-Square X^2 (p-value)
Diarrhea	14	10	5	33	.004
Joint Stiffness	43	51	55	72	.04
Irregular heart rate	0	4	5	24	.002
Weakness	29	22	15	52	.001
Muscle Pain	43	40	30	69	.002
Confusion	10	14	5	30	.02
Word Finding	29	37	16	50	.02
Sleep Problems	57	55	20	75	.001
Breathing trouble	5	16	0	23	.04
Body tingling	33	30	25	58	.004
Twitching	19	22	15	41	.03
Anxious	24	36	10	50	.005
Rapid Heart Rate	14	12	0	31	.005

Figure 11. Health Symptom Results by Pesticide groups



Task 3c. Exposure Assessment analyses for pesticides and PB will be completed.

Exposure assessments of individual and combined classes of pesticides are now complete and have allowed assessment of dose-response relationships with health and cognitive functioning. Mr. William Bradford, lead author of the Environmental Exposure Report – Pesticides (EER), assisted with these exposure estimates. Results of analyses follow below including descriptive analyses for pyridostigmine bromide (PB) exposure. Total number of PB pills ingested as reported on the study questionnaire is presented in the table below. Analyses comparing total PB pills ingested by cognitive domains were nonsignificant.

Table 17. Pyridostigmine Bromide Exposure Categories for 159 Study Participants

PB Exposure	**Frequency**	**Percent**
No	40	25
Yes	117	74
Unknown	2	1
Total	159	100
PB Dosage (Total Tablets)	**Frequency**	**Percent**
1-5	29	25
6-20	46	40
21-40	21	18
41-90	19	15
91+	3	2
Total	117	100

Individual pesticide exposures for the 12 pesticides of potential concern (see figure3) for the study sample of 159 recruited study participants were categorized based on questionnaire reporting and past PCI interviews. The results are presented in the table below. This provided the ability to assess neuropsychological and health symptom reports in higher exposed individuals compared with those with less exposure in a dose-dependent manner. Regression

analyses were performed to assess the separate and then combined impacts of high PB and pesticide exposed individuals, particularly with regard to combinations of PB and other carbamates (bendiocarb, methomyl, and propoxur) and organophosphates (azamethiphos, chlorpyrifos, diazinon, dichlorvos and malathion). Results are presented below.

Table 18. Exposure Assessment for Pesticides of Potential Concern for 159 Study Participants.

Pesticide	Low Exposed	High Exposed	Percent high Exposed
DEET	**90**	**69**	**43**
Permethrin	**121**	**38**	**24**
d-phenothrin	**155**	**4**	**3**
Azamethiphos	**139**	**20**	**13**
Chlorpyrifos	**114**	**45**	**28**
Diazinon	**119**	**40**	**25**
Dichlorvos	**103**	**56**	**35**
Malathion	**111**	**48**	**30**
Methomyl	**92**	**67**	**42**
Propoxur	**146**	**13**	**8**
Bendiocarb	**126**	**33**	**21**
Lindane	**116**	**43**	**27**

Exposures ranged from 3 to 43 percent depending on the pesticide product. These results suggest that PCI Gulf War veterans showed the highest percentages of increased risk exposures for the pesticide products that were most commonly available and likely to be exposed in the general military population during the Gulf War (see figure 4). These products include pest strips (dichlorvos), fly baits (methomyl) and personal repellants (DEET). The

more restricted organophosphate and carbamate pesticides products followed second in terms of increased exposures in these PCIs resulting from fogging and spraying duties of their occupational duties during the war (see figure 5). Given that study participants were exposed to each of the 12 POPCs, it was feasible to study exposure to each of the pesticides of potential concern in this study sample.

In order to assess which POPC was the best predictor for performance in each cognitive domain, stepwise regression analyses were performed by comparing each POPC by cognitive domain (attention/executive, psychomotor, visuospatial, memory, mood and motivation). Results are presented below and suggested that dichlorvos (pest strips) was the best predictor for the psychomotor domain ($p = .01$); and methomyl (fly bait) and lindane (delouser) were the best predictors for the mood and motivation domain ($p<.001$ and $p=.005$) and that diazinon was the best predictor for the visuospatial domain ($p=.03$).

When comparing individual tests within the significant domains, the Continuous Performance Test (CPT) mean reaction time was significantly associated with dichlorvos exposure (see figure 9). While higher endorsements on the Profile of Mood States (POMS) subscales of depression and fatigue were significantly associated with lindane exposure and higher endorsement on the subscales of depression, fatigue, tension, anger, and confusion were significantly associated with methomyl exposures. These analyses were still significant when the psychiatric diagnosis of PTSD was included in the model along with age, education and gender (see Table 19). Conversely, higher exposure to diazinon was significantly associated with better performance on the Rey-Osterrieth Complex figure test ($p = .001$). It is of interest to note that the means of both the high and low diazinon exposed groups could be considered clinically below normal for this task thus making this finding seem likely due to chance (see figure 10).

Figure 9. CPT Mean Reaction time Performance with Dichlorvos Exposure

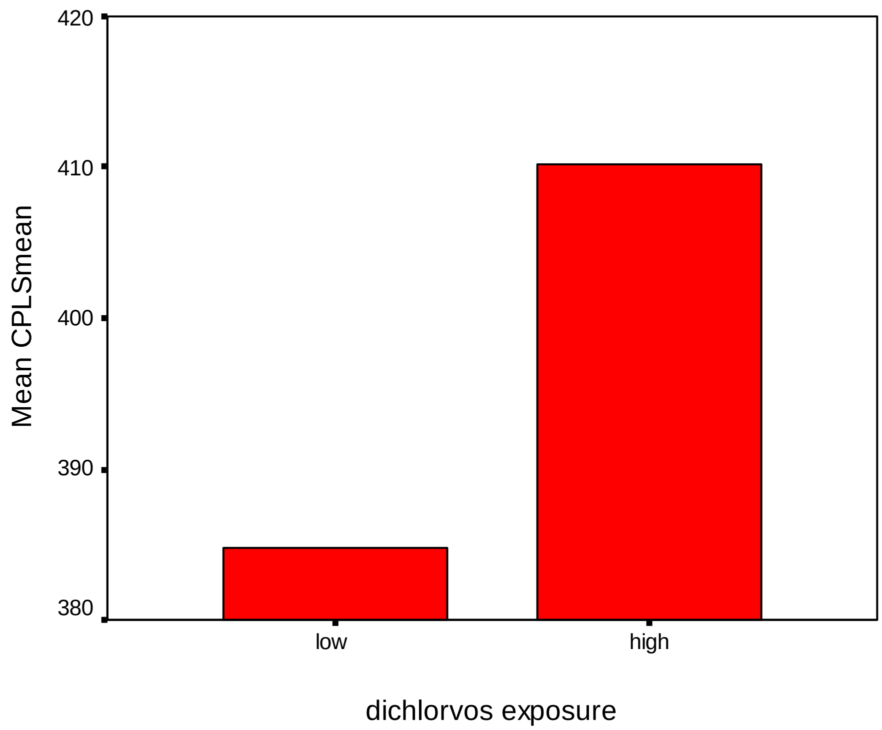


Figure 10. Diazinon Exposure by Rey-O Performance

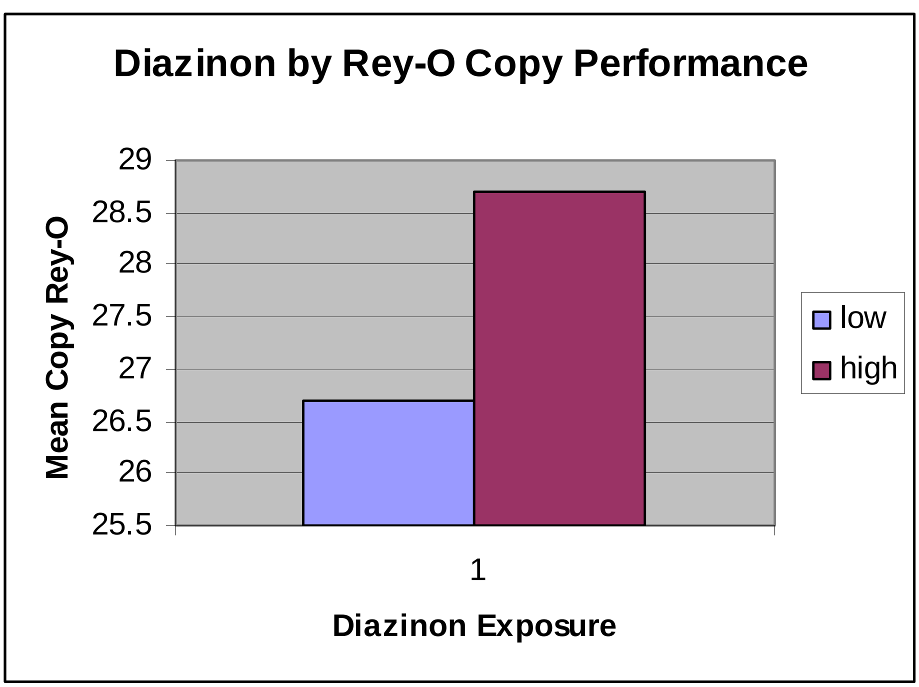
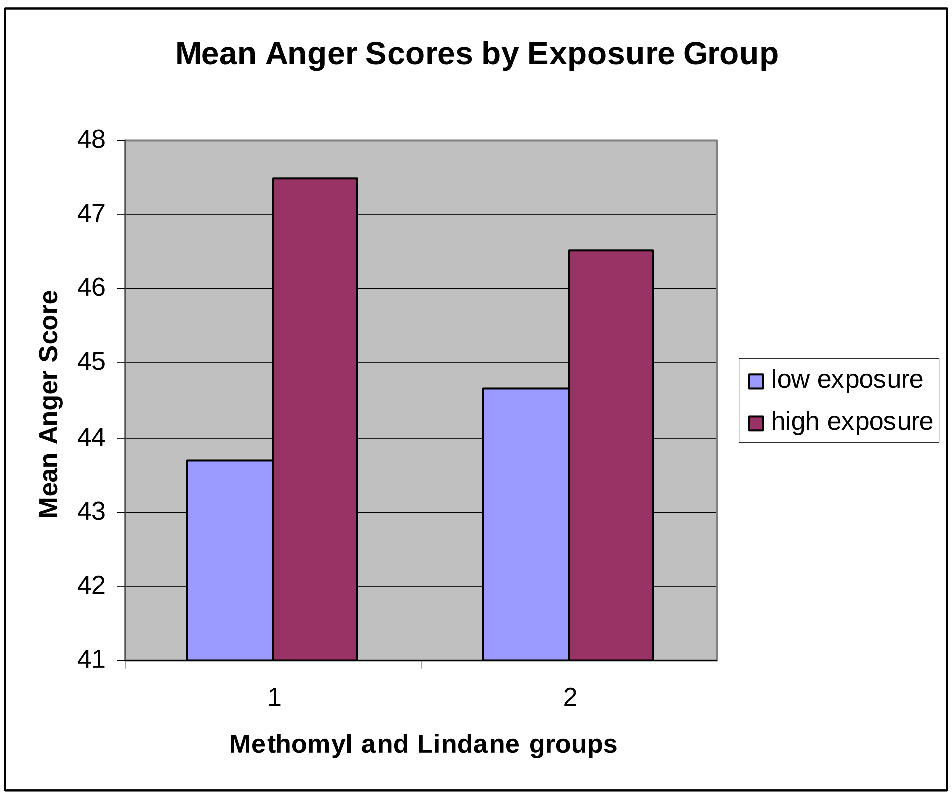
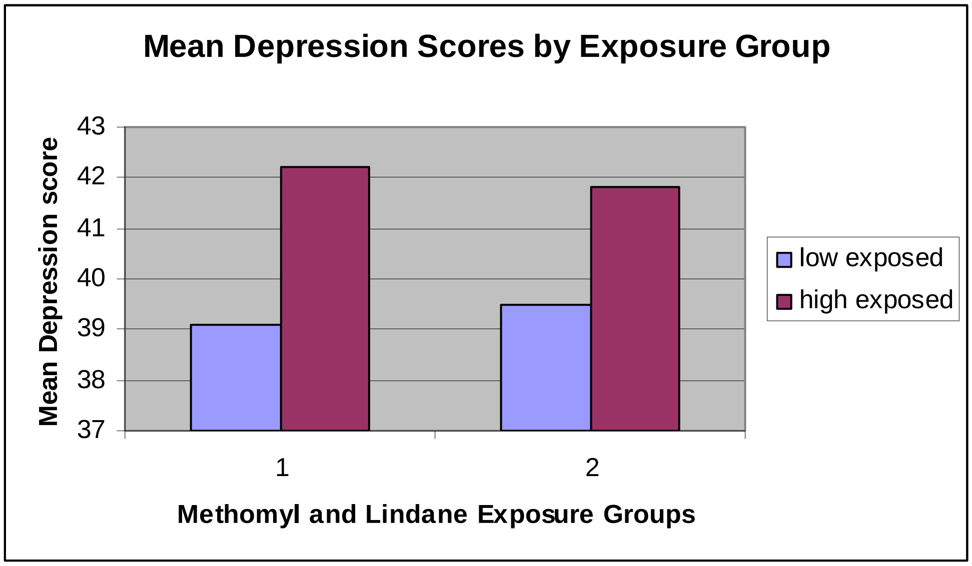


Table 19. Methomyl and Lindane Mood related Regression Analyses

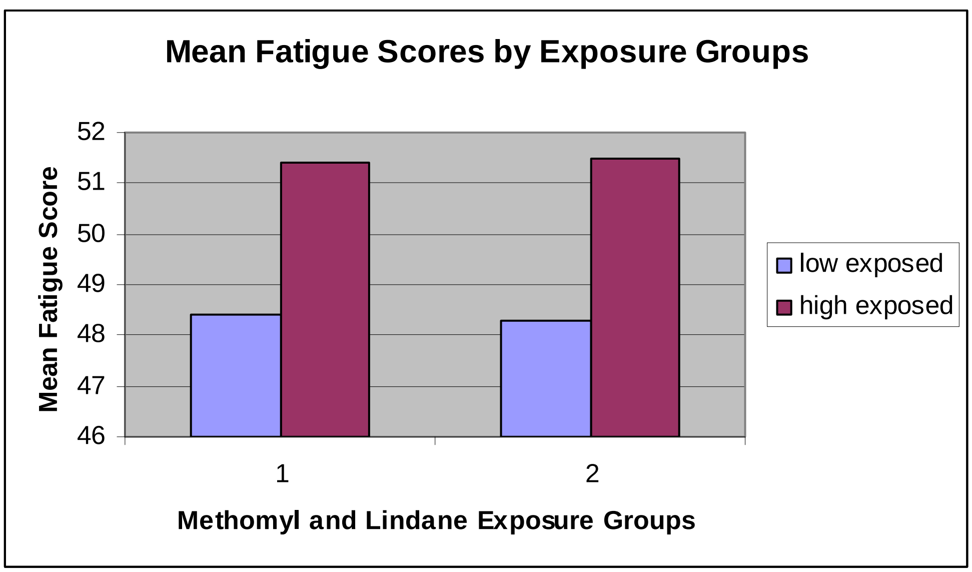
POMS subscale	Methomyl Beta	Methomyl Significance	Lindane Beta	Lindane Significance	PTSD Beta	PTSD Sign.
Tension	**.262**	**.000**	**.262**	**.06**	**.305**	**.000**
Depression	**.182**	**.02**	**.153**	**.04**	**.329**	**.000**
Fatigue	**.178**	**.01**	**.161**	**.03**	**.318**	**.000**
Anger	**.227**	**.005**	**.106**	**.18**	**.117**	**.135**
Confusion	**.159**	**.04**	**.076**	**.31**	**.293**	**.000**



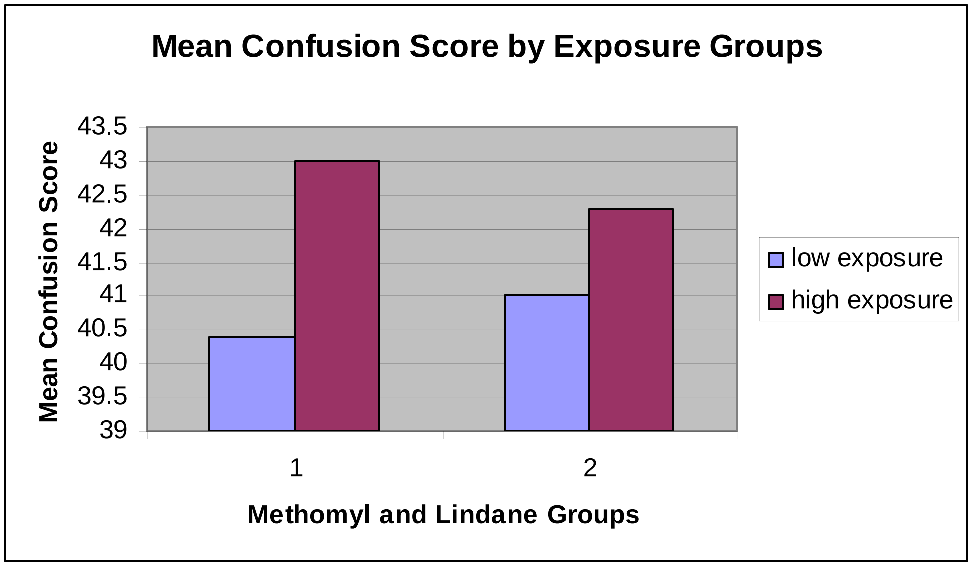
Group 1 = Methomyl Exposed (p =.005), Group 2 = Lindane Exposed Group (p =.18)



Group 1 = Methomyl exposure (p= .02) Group 2 = Lindane exposure (p = .04)



Group 1 = Methomyl exposure (p = .01); Group 2 = Lindane exposure (p =.03)



Group 1 = Methomyl exposure (p =.04); Group 2 = Lindane exposure (p = .13)

Analyses comparing combined pesticides of potential concern (POPC) with health symptom reporting suggested a significant association between total health symptoms reported and total organophosphate exposure (Table 20) when compared as a dichotomous hi/low variable. Total health symptoms were also significantly associated with increasing hazard index for combined carbamate exposures and with combined acetylcholinesterase exposure quartiles (Table 21). There were no significant linear associations between hazard indexes for organophosphates or carbamates on the neuropsychological domains.

In terms of individual pesticides, chronic rash was significantly associated with high exposure to methomyl (p =.05, OR = 2.8), azamethiphos (p=.03; OR = 4.8), diazinon (p=.05; OR = 4.9) and chlorpyrifos (p=.003; OR=4.5). In addition, sinus allergies were significantly associated with methomyl exposure (p=.01; OR=3.3) and arthritis diagnosis was associated with diazinon exposure (p=05; OR = 2.7) while neurological diagnosis was significantly associated with dichlorvos exposure (p=.02; OR =4.5). Pyridostigmine bromide was significantly associated with muscle pain (p=.05; OR = 1.7) and with joint pain (p=.05; OR = 1.8).

Table 20. Organophosphate Exposure vs. Mean Total Health Symptoms

	High OP risk	Low OP risk	Significance
Mean Health Symptoms	11.8	7.4	.05

Table 21. Regression analyses comparing combined Carbamate and Aceytlcholinesterase Hazard Indexes by Total Health Symptoms

	Carbamate Beta	Carbamate Significance	AchE quartiles Beta	AchE quartiles Signficance
Total Health Symptoms	.235	.002	.163	.05

Table 22. Health Symptoms by Individual POPCs.

Symptom	POPC	% high	Sig. value	Odds ratio
Chronic Rash	Methomyl	31	.05	2.8
Chronic Rash	Azamethiphos	50	.03	4.8
Chronic Rash	Chlorpyrifos	40	.003	4.5
Chronic Rash	Diazinon	36	.03	3.2
Arthritis	Diazinon	50	.05	2.7
Sinus Allergy	Methomyl	50	.01	3.3
Neuro disease	Dichlorvos	16	.02	6.1
Muscle pain	PB	55	.05	1.7
Joint stiffness	PB	65	.05	1.8
IBS	Khamisiyah	22	.05	6.1

Task 3d. Annual reports of progress will be written.

This report is the fifth and final report written for this project. The first report was submitted on February 28, 2005 and accepted on February 9, 2006. The second report was submitted on February 28, 2006 and accepted on July 7, 2006. The third report was submitted February 28, 2007 and accepted June 2007. The fourth report was submitted February 28, 2008.

Task 4a. Analyze subject characteristics of individuals who were lost to follow-up.

There were 293 PCIs interviews included in the DoD's Environmental Exposure Report (EER) pesticides. The goal of the study was to recruit 160 PCIs from the original DoD cohort. In total, 159 total study participants were recruited for this study thus leaving 134 PCIs that were not recruited for the current study. A review of the few demographic details in the original DoD interviews with the non-recruited PCIs are listed in table 23 below and show that there were no significant differences between the groups for demographics, job duties during the Gulf War or health symptom reporting.

Table 23. Participant and Non-Participant Demographics.

	Participants (% reporting)	Non-participants (% reporting)	Significance
Female	13	19	ns
Male	87	81	ns
Active Duty	9	17	ns
Took PB pills	74	71	ns
Applied Pesticides	68	65	ns
Reporting health problems	47	46	ns
Preventive Medicine Specialist	69	72	ns
Military Police	8	10	ns
Environmental Scientist	12	6	ns
Entomologist	6	8	ns
Other Job	5	3	ns

KEY RESEARCH ACCOMPLISHMENTS

- A pool of potential study participants was identified from a group of previously interviewed pest control personnel deployed to the Gulf War.
- Previous interviews by the Deployment Health Support Directorate (DHSD) regarding pesticide and pyridostigmine bromide (PB) exposure were obtained and used to classify these individuals into high and low exposure groups.
- Telephone interviews were performed and resulted in only a seven percent refusal rate of live calls and completion of the targeted 160 total completed exposure surveys of PCIs.
- Potential study participants were categorized based on current residence and re-categorized when residence changed.
- Current health symptoms were identified and categorized into symptom clusters based on initial telephone interviews.
- PCIs responding to the SRBI interviews were categorized into high and low exposure groups for pesticides and PB and a pool of potential subjects were targeted for recruitment based on residence location and exposure category.
- One hundred and fifty nine study participants were recruited and completed the study protocol including cognitive evaluations, psychological interviews and exposure questionnaires. This resulted in a 99% recruitment rate for years 1-4.
- All of the study recruitment trips were greeted with interest and willingness to participate by the contacted PCIs. This is encouraging for further recruitment efforts for the recently funded follow-up Pesticides MRI study. It appears that GW veterans continue to be interested in responding to surveys regarding health symptoms and are cooperative when asked to complete neuropsychological evaluations.
- It was determined that the study design allowed for collection of all relevant data and could be accomplished in recruitment trips throughout the country.

- Initial exposure assessments of the 12 pesticides of potential concern (POPC) and pyridostigmine bromide (PB) showed that analyses of individual pesticides with cognitive and health functioning would be possible since the larger study sample was obtained.
- Analysis were performed of the total 159 study participants and showed lower mean reaction times and mood related scores in the high pesticide x high PB group compared with the other three exposure groups.
- Psychiatric diagnoses including post-traumatic stress disorder and current major depression were assessed and found to be slightly elevated in this group of predominantly non-treatment seeking veterans while rates of chronic fatigue syndrome and multiple-chemical sensitivity were low when assessed by clinical interview. Analyses were performed controlling for PTSD to control for any potential study confounds.
- Health symptom reports were compared among the total sample of 159 study participants by using the health symptom checklist. These analyses showed higher symptom reporting in high pesticide exposed individuals relative to low pesticide exposure. Specifically, high exposures was related to GI disturbance, weakness, joint pain, word finding difficulty, sleep disturbance, skin rash and muscle pain. When comparing the four groupings of high and low pesticide x PB groupings, the CMI diagnosis was significantly higher in the high pesticide / high PB groupings as well as the CMI subscales of mood/cognition and fatigue.
- Health Symptom diagnoses were compared in Khamisiyah exposed individuals. The results suggested that individuals with Khamisiyah notification were significantly more likely to be diagnosed with irritable bowel syndrome than those without such notification.

- The elevated health symptom reports were much greater than the original SRBI telephone interviews where each PCI was asked to report their most prominent health symptoms or medical diagnoses. Medical diagnoses were higher in the high pesticide exposed group but not significantly so for most diagnoses. Overall, this sample of GW veterans appeared to show slightly higher rates of asthma, allergies, and hypertension than reported in general population rates for their age.
- The main study hypotheses that combinations of pesticides and pyridostigmine bromide exposed Pest Controllers would perform worse on cognitive testing and report more health symptoms was confirmed in this study as shown by worse reaction time performance and mood related functioning in this group. This finding correlates with other classic studies of residual sequelae from pesticide exposures. In addition, visual memory functioning was found to be significantly different among the exposure groups with the high pesticide x low PB group showing the worst performance overall.
- Comparisons of individual pesticides of potential concern (POPC) were assessed and showed that some of the pesticide exposures were particularly good predictors of specific mood and cognitive difficulties. This appeared to be the case for mood performance in relation to methomyl and lindane exposure and dichlorvos for mean visual reaction time performances.

REPORTABLE OUTCOMES:

Publications

1. Pesticide Exposure, Health Functioning and Neuropsychological Outcome in Gulf War I Veterans (Abstract). Sullivan, K., Krengel, M., Thompson, T., Proctor, S.P. & White, R.F., International Neuropsychological Society, 34th Annual Meeting Program and Abstract Book, 2006: 208.
2. Cognitive functioning in Gulf War I veterans exposed to Pesticides, Pyridostigmine Bromide and Khamisiyah Weapons Depot (Abstract). Sullivan, K., Krengel, M., Thompson, T., Comtois, C., & White, RF. International Neuropsychological Society, 35th Annual Meeting Program and Abstract Book, 2007: 210.
3. Qualitative Findings in Complex Figure Drawing in Military Pesticide Applicators from the Gulf War. (Abstract). Sullivan, K., Janulewicz, P., Krengel, M., Comtois, C., & White, R. International Neuropsychological Society, 35th Annual Meeting Program and Abstract Book, 2007: 209.
4. Proctor SP, Gopal S, Imai A, Wolfe J, Ozonoff D, White RF. Spatial analysis of 1991 Gulf War troop locations in relationship with postwar health symptom reports using GIS techniques. Transactions in GIS 2005; 9(3): 381-396.
5. Proctor, S.P., Heaton, KJ, Heeren, T. & White, R.F. Effects of sarin and cyclosarin exposure during the 1991 Gulf War on neurobehavioral functioning in US Army veterans. Neurotoxicology. 2006; 27(6): 931-939.
6. Comtois, C., Sullivan, K., Krengel, M. & White, R.F. (Abstract). Health Symptom Correlates among Military Pesticide Applicators from GWI. Massachusetts Neuropsychological Society Annual Meeting, May 2007.
7. Pinto, L., Sullivan, K., Krengel, M., Powell, F., Killiany, R. & White, R.F. (Abstract). Structural MRI Findings Correlate with High Symptom Status Among Gulf War Veterans. Massachusetts Neuropsychological Society Annual Meeting, May 2007.

8. Krengel, M, Comtois, C, Sullivan, K & White RF. (Abstract). The Cognitive Correlates of Chronic Multisymptom Illness in GWI Military Pesticide Applicators. International Neuropsychological Society, 36th Annual Meeting Program and Abstract Book, 2008: 103.

<u>Invited Presentations</u>

1. Krengel, M, Sullivan, K & White, R.F. Neuropsychological Functioning and Health Symptom Report in Pesticide and Pyridostigmine Bromide Exposed Gulf War Veterans. Stanford Research Institute, Palo Alto, CA, February 12, 2007.
2. Krengel, M. The Cognitive implications of exposure to Blast Munitions presented at the Neuro- Rehab Management conference, Boston, MA November, 2007
3. Krengel, M., Sullivan, K., Grande, L. Neuropsychological Patterns of Blast and non-blast related Traumatic Brain Injury in OIF/OEF veterans. International Neuropsychological Society symposium, Hawaii, February 8, 2008.
4. White, R.F., Heaton, K, Krengel, M, Ringe, W, Vasterling, J. Neuropsychiatric Aspects of Combat Exposures (Blast Injuries, TBI and PTSD), International Neuropsychological Society symposium, Hawaii, February 8, 2008.
5. Krengel, M. The Health Symptoms of returning veterans. Paper presented to the Boston Acquired Brain Injury Support Group. Boston, MA September 6, 2008
6. Krengel, M. What works: Addressing Post-traumatic stress disorder and traumatic brain injury with returning veterans and their families. Paper presented to the National Behavioral Health Conference and Policy Academy on Returning Veterans. Washington, D.C. August 11, 2008
7. Krengel, M. Identification of services/supports for OIF/OEF veterans with mild TBI. Paper presented to the Federal TBI Program Servicemembers with TBI Summit meeting. Washington, DC. April 1, 2008

Manuscripts in preparation: (from previous DOD funding sources)

1. Proctor et al., Environmental and Occupational Exposure Predictors of Multiple Chemical Sensitivity in Gulf War Veterans Assessed via a Validated Screening Instrument.
2. Proctor, Sullivan et al., Validation of a Structured Neurotoxicant Assessment Checklist in Military Populations.

Planned Manuscripts:

1. Krengel et al., Cognitive Functioning in military pesticide applicators from the Gulf War.
2. Sullivan et al., Health Symptom Report in pesticide applicators from the Gulf War.
3. Sullivan, White et al., Lower white matter volumes predict higher health symptoms in Gulf War veterans.

Funding:

1. In June 2004, Drs. White, Krengel, Sullivan, and Proctor submitted a Merit Review grant application (Dr. White PI) to the Department of Veterans Affairs entitled "Structural Magnetic Resonance Imaging and cognitive correlates in Gulf War veterans." This study will further define neurological functioning in a previously followed cohort of treatment-seeking GW veterans and will allow for comparison of reported GW exposures with brain white matter volumes. This grant was funded and recruitment efforts are now complete. Preliminary results to date suggest lower white matter volumes in the high symptom Gulf War veterans compared with low symptom reporting GW veterans.

2. In September 2006, Drs. Krengel, Sullivan, and White submitted a VA Merit review grant (Dr. Krengel, PI) to examine the continued health effects of GW veterans with cutting edge neuroimaging techniques in treatment-seeking GW veterans. This grant was not funded.

3. In February 2007, Drs. Sullivan, Krengel, and White submitted a grant to the DoD Gulf War Veterans Illness Research Program (GWVIRP) under the congressionally directed medical research program (W81XWH-06-GWVIRP) for a follow-up study to the currently funded study of military pesticide applicators in order to compare structural brain imaging in the high and low pesticide exposed groups. This proposed grant will focus on whether acetylcholinesterase inhibiting pesticides including organophosphates could be among the contributing factors to some of the undiagnosed illnesses in GW veterans by comparing objective biomarkers of exposed veterans and comparing brain white matter volumetrics between the groups. This grant was listed as an alternate for funding and was recently funded in part for a scaled down study. This study is currently funded for an 18-month period to study 30 PCI veterans. This study will follow-up on the preliminary findings of the recently completed VA Merit Review study of Drs. White, Sullivan and Krengel which found lower white matter volumes in high symptom reporting veterans. If the currently funded study can determine a pattern of high health symptom reporting, high AchE exposure and lowered brain volumes, we will be one step closer to obtaining a biological marker for Gulf War related illness and steering potential treatment options for those still coping with symptoms.

4. Drs. Krengel and Sullivan submitted two recent grants (Sept. / Oct. 2007) to the congressionally directed medical research program (CDMRP) to study the residual effects of blast-related traumatic brain injury (TBI) in Iraq (OIF) and Afghanistan (OEF) returnees. The first grant was aimed at treating veterans living in rural areas and included a cognitive behavioral treatment (CBT) administered through televideo equipment in the veterans homes. This grant is currently listed as an alternate for funding. The second grant included establishing a database of blast and non-blast related sequelae in TBI diagnosed returnees through a collaboration of five polytrauma network site (PNS) clinics around the country. This grant was not recommended for funding.

CONCLUSIONS:

Results of neuropsychological analyses in the complete sample of 159 study participants broken down into the four pesticide x PB exposure groups indicated a significant effect of lowered mean reaction times and increased mood complaints in the high pesticide x high PB exposed group compared with the three other exposure groups. These results lend support to the initial study hypothesis that multiple chemical exposures have contributed to the continued health complaints of Gulf War veterans. In addition, it appeared that the combined impact of multiple pesticide exposures without exposure to PB, contributed significantly to worse performance on a complex visual memory task. Some individual pesticides also appeared to be the best predictors and thus have more of an independent effect on cognition and mood functioning. Specifically, high dichlorvos exposure from pest strips was significantly associated with mean reaction time performance on the continuous performance test. While the fly bait methomyl and the delousing agent lindane were associated with mood functioning on several scales of the Profile of Mood States test even when PTSD was controlled for in the statistical model. These findings suggest an independent effect for these specific pesticides on information processing speed and mood performances. These findings appear to correlate with studies performed by Stevens et al., (1995) and Steenland et al., (1994) and more recently by Bazylewicz-Walcczak et al., (1999), suggesting similar subtle effects on cognition and mood with chronic low-level exposures to combinations of organophosphate pesticides in professional pesticide applicators, greenhouse workers, and sheep dipping farmers.

In addition, health symptom reporting was also significantly associated with the high pesticide x high PB group with regard to joint stiffness, muscle pain and weakness, sleep disturbance, gastrointestinal disturbances, mood and word-finding difficulty. When clinical diagnoses and health were compared, a slightly elevated rate of PTSD and depression were noted as well as asthma, allergies, and hypertension in both exposure groups. In addition, this study documented

neurological diseases of concern in a small group of the study participants including neuropathy (n=7), non-malignant brain tumors (n=2) and multiple sclerosis (n=1). Overall, these findings of motor slowing, mood complaints, allergies, asthma, hypertension and neurological diseases in this group of higher exposed pest control military veterans suggests that clinicians treating GW veterans should consider these domains when assessing the health and functional well-being of these aging veterans. Although the neurological diagnoses of concern were small in number, the known risk of Gulf War veterans with increased brain cancer (Bullman et al., 2005) and ALS (Horner et al., 2003) from other studies suggests that Gulf War veterans complaining of neurological difficulties should be taken seriously and followed very closely.

Our preliminary findings from the SRBI interviews alone suggested that GW veterans exposed to varying levels of pesticides and PB continued to report health symptoms, including high blood pressure, cardiovascular disease, skin rashes, memory problems and stress reactions. These results were confirmed when more in-depth health symptoms were ascertained from the study questionnaire with the complete group of 159 study participants. Of interest, veterans who participated in the SRBI telephone surveys reported significantly more physical than emotional symptoms. However, when interviewed in-person several of the study participants met clinical criteria for post-traumatic stress disorder (8.8%) and depression (10.1%). This finding stresses the importance of face-to-face interviews and evaluations with study participants in addition to postal questionnaires or telephone surveys. In addition, PTSD was significantly associated with mood and reaction time analyses in this study and was therefore included as a covariate in all analyses in order to control for this potential study confound. Depression was considered a study outcome rather than as a potential study confound due to the documented effect of some pesticides on mood functions (Stevens et al., 1995; Steenland et al, 1994). This finding was further documented in this study as mood related functions including tension, depression, anger, confusion and fatigue were significantly predicted by exposure to the fly bait methomyl and fatigue and depression were significantly predicted by exposure to the delouser lindane.

It still remains of particular clinical relevance that these largely non-treatment seeking veterans continue to report significant physical symptoms many years following their deployment. By documenting subtle changes in cognitive status in conjunction with health concerns in this unique group of Gulf War veterans, the effects of exposure to neurotoxicants while in the Gulf has been further elucidated. This study confirms the conclusion of the OSAGWI health risk assessment and the RAND pesticide report which suggested that the acetylcholinesterase inhibiting pesticides including organophosphates and carbamates could be among the contributing factors to some of the undiagnosed illnesses in GW veterans. In addition, this study suggests that specific pesticides may have been particularly influential with respect to continued mood related complaints (methomyl, lindane) and worse information processing speed (dichlorvos) while combinations of similarly acting pesticides predicted other health symptom complaints (chronic skin rash with methomyl, azamethiphos, diazinon and chlorpyrifos exposures). The fact that these pesticides include flybaits (methomyl), pest strips (dichlorvos) and delousers (lindane) which were often used by general military personnel in addition to certified pesticide applicators, suggests that the findings of this study are applicable to the larger cohort of Gulf War veterans. These results when combined with the estimate from the OSAGWI health risk assessment that 41,000 general military personnel from the Gulf War might have been overexposed to pesticides during their deployment, suggest that a cause for continued complaints of undiagnosed illnesses in a subgroup of the nearly 140,000 symptomatic Gulf War veterans may be the overexposure of neurotoxicants.

Recommendations:

- Pesticide applications should be performed by trained certified applicators only when necessary to protect troops from hazardous pests but also to protect them from undue exposure to potentially synergistic classes of pesticides.
- Pest-strips should never be used in enclosed areas where soldiers work or sleep for extended periods of time as potentially toxic levels of exposure may occur.

- Fly bait crystals should be handled carefully and should not be used near food (Several individuals reported that fly baits were often used in tins on top of food service tables to control flies during their deployment).
- Adequate personal protective equipment should be provided to all certified pesticide applicators. This was identified as a potential problem for some reservist units who reported not having adequate gloves, respirators or masks to use during pesticide applications. This was a particular concern for military police who reported delousing enemy prisoners of war for 8-10 hour shifts with the highly toxic organochlorine lindane with either no respirators at all or no replacement cartridges for the respirator thus making them non-usable in several instances.
- Military pesticide applicators should be regularly assessed for decreased cholinesterase levels during health screenings to assess whether preventive measures should be taken (i.e. rest periods from performing pesticide application duties).
- DoD should consider phasing out more of the known toxic pesticides for less toxic alternatives. This is particularly important for the organochlorine delousing agent lindane, which is known to persist in the environment for long periods of time and to bioaccumulate.
- Gulf War veterans complaining of neurological symptoms should be taken very seriously and followed closely by their healthcare providers.
- Functional brain imaging studies may help further elucidate the nature of the subtle cognitive differences in information processing speed, visual memory and mood found in this cohort of documented pesticide exposed individuals.

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Appendix:

T. MCQUEENY, K. LISDAHL MEDINA, A.D. SCHWEINSBURG, M. COHEN-ZION, B.J. NAGEL & S.F. TAPERT. Effects of Alcohol and Marijuana Use During Adolescence on Hippocampal Asymmetry and Cognitive Functioning.

Objective: Memory deficits have been reported in adolescents with heavy alcohol and marijuana use, yet the impact of these substances on hippocampal development remains unclear. In addition, relationships between hippocampal asymmetry and memory function have not been explored in substance involved adolescents. This study examined relationships between right > left (R>L) hippocampal asymmetry and cognitive functioning in alcohol and marijuana using adolescents.

Participants and Methods: Participants (15-18 years-old) were 16 alcohol using (Alc) teens, 26 marijuana and alcohol using (MJ-Alc) teens and 21 demographically similar controls. Hippocampal volumes were obtained through manually traced structural magnetic resonance images. All data were collected after at least 2 days of abstinence from all substances.

Results: After controlling for age and intracranial volume, group differences in asymmetry were observed ($p < .02$). Post-hoc analyses revealed that Alc teens had greater R>L asymmetry ($p < .05$) than both controls and MJ-Alc teens, for which more L>R asymmetry was observed. Among controls only, individuals with more R>L asymmetry performed better on verbal learning ($r = .45$, $p < .05$) whereas superior visual memory performance was related to greater L>R asymmetry ($r = -.54$, $p < .01$).

Conclusions: Alcohol using teens exhibited greater right versus left hippocampal asymmetry than other groups. The functional relationship between verbal and visual memory and hippocampal asymmetry was abnormal among substance using adolescents compared to non-drug using controls. These findings suggest differential effects of alcohol and combined marijuana and alcohol use on the relationship between hippocampal morphometry and learning and memory performance.

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K.L. MEDINA, K.L. HANSON, A.D. SCHWEINSBURG, M. COHEN-ZION & S.F. TAPERT. Neuropsychological Functioning in Adolescent Marijuana Users: Subtle Deficits Detectable After 30 Days of Abstinence.

Objective: In adults, studies examining the long-lasting cognitive effects of marijuana use demonstrate subtle deficits in attention, executive function, and memory. However, since neuromaturation continues through adolescence, these results cannot necessarily generalize to adolescent marijuana users. Therefore, the goal of the present study was to examine neuropsychological functioning in abstinent marijuana-using and demographically similar control adolescents.

Participants and Methods: Data were collected from 65 adolescent marijuana users (n=31, 26% female) and controls (n=34, 27% female) aged 16-18. Extensive exclusionary criteria included independent psychiatric, medical, and neurologic disorders. Substance use information and neuropsychological assessments were collected after 30 days of monitored abstinence. Dependent variables were composite scores for: psychomotor speed, visuospatial skills, complex attention, story memory, verbal list learning, verbal fluency accuracy, planning and sequencing, and problem solving.

Results: After controlling for lifetime alcohol use and gender, adolescent marijuana users demonstrated significantly poorer planning and sequencing ability ($\beta = -.78$, $p < .002$), complex attention ($\beta = -.37$, $p < .05$), and slower psychomotor speed ($\beta = -.49$, $p < .05$) compared to demographically similar controls. No significant gender-by-group interactions were observed.

Conclusions: The general pattern of results suggested that even after 30 days of monitored abstinence, adolescent marijuana users continue to demonstrate subtle deficits in planning and sequencing, complex attention, and psychomotor speed compared to non-marijuana using teens. Thus, marijuana use during adolescence may negatively impact neuromaturation and cognitive development. Implications include the need for psychoeducation aimed at informing adolescents and parents of the potential long-term cognitive consequences of heavy marijuana use, as well as longitudinal studies to help rule out premorbid influences.

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A.D. SCHWEINSBURG, K.L. MEDINA, T. MCQUEENY, B.C. SCHWEINSBURG & S.F. TAPERT. An FMRI Study of Residual and Persisting Abnormalities in Adolescent Marijuana Users.

Objective: Research suggests recovery from the neurocognitive impact of marijuana use within a month of abstinence among adults. We previously demonstrated altered functional magnetic resonance imaging (fMRI) response to spatial working memory (SWM) in heavy marijuana using (MJ) adolescents after 28 days of abstinence, but the influence of recency of use has not yet been explored in detail. In this study, we compared fMRI response during SWM between MJ teens with brief and sustained durations of abstinence.

Participants and Methods: Participants were 15-18 years old, including 15 MJ teens (33% female) who had used 2-44 (mean=4) days prior to scanning (MJ-recent), and 15 MJ teens (27% female) who had been abstinent for at least 27 (mean=35) days (MJ-abstinent). Groups were similar on demographic and substance use characteristics, and had no psychiatric or medical disorders. Teens performed a SWM task during fMRI acquisition.

Results: Groups performed similarly on the SWM task, but MJ-recent showed more fMRI response in left superior and medial prefrontal cortices, bilateral insula, left superior temporal cortex, and right superior parietal cortex. MJ-abstinent had more response in the right precentral gyrus (clusters > 1328 microliters, $p < .05$).

Conclusions: Results show that recent marijuana using adolescents have more brain response than abstinent users during a spatial working memory task. Though cross-sectional, this evidence could suggest less compensatory neural response as the brain adjusts to the absence of marijuana through early abstinence. Longitudinal studies are needed to characterize the potential neural recovery during early abstinence from marijuana.

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K. SULLIVAN, M. KRENGEL, T. THOMPSON, C. COMTOIS & R. WHITE. Cognitive Functioning in Gulf War I Veterans Exposed to Pesticides, Pyridostigmine Bromide and Khamisiyah Weapons Depot.

Objective: One theory for the continued health complaints in GW I veterans is the combination of multiple chemical exposures. The goal of this study was to evaluate the relationship of the combined exposures of pesticides, pyridostigmine bromide (PB) and sarin on the cognitive functioning of GW I veterans.

Participants and Methods: Study participants included a unique group of 100 pesticide control personnel from the GW including pesticide applicators (high-exposed group) and preventive medicine specialists (low-exposed group). Each study participant completed a comprehensive battery of neuropsychological tests, psychological interviews and health symptom/exposure assessment questionnaires. It was hypothesized that individuals with high pesticide exposure would perform significantly worse on cognitive measures than a group of GW military personnel with low pesticide exposure. It was also hypothesized that multiple chemical exposures (PB, pesticides, sarin) would prove to be synergistic and/or additive in terms of decreased cognitive functioning.

more response than controls. Group differences remained after controlling for alcohol use. **Conclusions:** Despite comparable task performance, heavy marijuana using teens showed less learning-related brain response than controls, consistent with adult research. This pattern may indicate use of alternate strategies and greater rehearsal during resting blocks. Group effects were observed after 28 days of confirmed abstinence, which could suggest persisting marijuana-related changes or premorbid differences in brain functioning.

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K. SULLIVAN, M.H. KRENGEL, T. THOMPSON & R.F. WHITE. Pesticide Exposure, Health Functioning, and Neuropsychological Outcome in Gulf War I Veterans.

Objective: Current hypotheses regarding the sustained health complaints of Gulf War I (GW) veterans invoke exposure to multiple chemical exposures. In order to explore this notion, we examined veterans responsible for pesticide control for their various military units during the GW. **Participants and Methods:** GW pesticide control personnel were exposed to several different types of pesticides and at larger doses than general military personnel, making them a unique group to study. Veterans were divided into high and low exposure groups. Study participants responded to a self-report survey regarding their current health concerns, psychological functioning and cognitive complaints. They were given a comprehensive neuropsychological assessment, including measures of mood, motor functioning, short-term memory and attention. **Results:** Preliminary analyses have been completed on 33 subjects. The veterans rank health symptoms such as skin rash, fatigue, and depression as significant complaints. Multiple chemical sensitivity and hypertension appeared to be significant in this group. In addition, chronic post-traumatic stress disorder was highly prevalent. When neuropsychological variables were analyzed, veterans with high exposures were significantly different from veterans with low exposures on motor functioning and reaction time. Further analyses revealed significant effects of pyridostigmine bromide (PB)on test scores in this domain. **Conclusions:** These preliminary results suggest that there are differences in neuropsychological variables between high and low pesticide and PB exposed groups. The relationship of exposure to health outcome will be discussed.

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M.J. TAYLOR, B.C. SCHWEINSBURG, A. GONGVATANA, O.M. AL-HASSOON, R.J. THEILMANN & I. GRANT. Microstructural Disruption ofWhite Matter Integrity in Recently-Detoxified Alcoholics Measured with Diffusion Tensor Imaging.

Objective: The goal of this study was to evaluate the impact of long-term alcoholism on the integrity of frontal and posterior cerebral white matter using diffusion tensor imaging (DTI). When axonal integrity is disrupted, an increase in diffusion and a concordant decrease in anisotropy can occur. The average diffusion coefficient (ADC) was hypothesized to be elevated in alcoholics relative to non-alcoholic controls, while fractional anisotropy (FA) was hypothesized to be lower in alcoholics. **Participants and Methods:** Thirty-three recently detoxified alcoholics (sober 2-6 weeks) in treatment at the VA San Diego Healthcare System and 16 non-alcoholic controls were evaluated using DTI. The groups were equated on age (mean = 46.5 years), education (mean = 13.3 years), gender (96% male), and ethnicity (86% Caucasian). Alcoholics met DSM-IV criteria for alcohol dependence and consumed a minimum of six drinks per day for the most recent five years. FA and ADC were calculated for regions of interest in frontal and posterior white matter. **Results:** ADC was significantly higher in alcoholics compared to controls in both frontal [$F(1,47)=4.38$, $p<.05$] and posteri [$F(1,47)=12.08$, $p=.001$] white matter regions. In addition, significa lower FA was present in posterior white matter of alcoholics compa to controls [$F(1,47)=10.04$, $p<.01$] with a similar trend in frontal whi matter. **Conclusions:** These results are consistent with studies usi other neuroimaging methods (e.g. structural MRI and MR spectros that suggest alcoholism-associated changes in white matter. Increa ADC and decreased FA could indicate disorganization of cerebral whi matter due to atrophy of both the myelin sheath and axon itself.

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N.P. VADHAN, C.L. HART, W.G. VAN GORP, M. HANEY R.W. FOLTIN. Does Smoked Marijuana Disrupt Decision-Mak in Experienced Users?

Objective: Recent preliminary findings from this laboratory indica that smoking a low to moderate Δ9-THC concentration cigarette i proved the performance of experienced marijuana users on a modifi Gambling task. The current study is a more extensive effort to cha terize the effects of marijuana intoxication on gambling task perfor ance in experienced marijuana smokers. **Participants and Metho** A within-participant double-blind design was employed in this stu Thirty-six marijuana users, who reported smoking approximately marijuana cigarettes per week, completed this 3-session outpatient stu sessions were separated by at least 72-hrs. Participants complete modified computerized gambling task once at baseline, and three ti after smoking a single marijuana cigarette (0%, 1.8%, or 3.9% Δ THC). Marijuana cigarettes were administered in a double-blind fa ion and the sequence of Δ9-THC concentration order was balanced acr participants. **Results:** Marijuana increased the time that particip required to complete the task, relative to placebo. However, de making (i.e., "advantageous" vs. "disadvantageous" card selection) a money earned on the task were unaffected by marijuana. Furtherm of all demographic and drug use variables examined, only level of ucation was associated with baseline performance on the modified Ga bling task. **Conclusions:** Smoked marijuana may slow down decisi making, but may not disrupt the advantageousness of decisions, experienced users. These data are consistent with other findings fr our laboratory that cognitive speed, but not accuracy, is affected by m ijuana smoking in experienced marijuana users.

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N.P. VADHAN, K.M. CARPENTER, C.L. HART, E.V. NUNES R.W. FOLTIN. Attentional Bias Towards Cocaine-Related Ve Stimuli in Cocaine-Dependent Individuals: A Comparison of Tre ment-Seekers and Treatment-Nonseekers.

Objective: When tested using modified Stroop color-naming tasks, d dependent individuals demonstrate attentional bias as shown by in ference from verbal stimuli associated with their drug of choice. We h previously reported that attentional bias, measured using a Stroop co naming task modified to include cocaine-related words, predicted tr ment outcome. The purpose of this study was to determine the r tionship between the treatment-seeking status of cocaine-depend individuals and attentional bias towards cocaine-related verbal **Participants and Methods:** We compared performance on a drug task between 32 participants who were seeking treatment for their caine dependence (25 males, seven females) and 15 participan were not seeking treatment for their cocaine dependence (14 m one female). **Results:** Treatment-seekers demonstrated slower reac times in the presence of drug-related words, relative to nondrug w (interference), whereas treatment-nonseekers demonstrated quic action times in the presence of drug-related words, relative to non

Reasoning, Symbol Search, Digit Symbol-Coding, WMS-III WordList, Verbal Paired Associates, and Logical Memory, Stroop, Cancellation H, Trail Making, COWAT, Fingertapping, Grooved Pegboard, and Dynamometer. Principal Components Analysis was performed to confirm domains of functioning assessed in these groups.
Results: Five factors with eigenvalues of 1 or higher explained 62% of the variance found in the welders group. These factors were consistent with the following domains: Immediate Verbal Memory, Delayed Verbal Memory, Attention and Executive Functioning, Mental Processing Speed, Motor Skills. All but one test had a factor loading above .5.
Conclusions: The short test battery used for screening welders with different exposure levels did assess the domains intended to be evaluated. Specific factor loadings for different tests will be shown.
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K.L. HANSON, M. LUCIANA & K. SULLWOLD. Reward-Related Decision-Making Deficits Among MDMA and Other Drug Users.
Objective: MDMA (3,4-methylenedioxymethamphetamine; Ecstasy) is a synthetic amphetamine derivative with mild hallucinogenic and stimulant effects. It is a known serotonin neurotoxin that may produce memory and executive dysfunction as well as impulsivity. However, few studies of MDMA users have examined reward-related decision-making, thought to be mediated by the ventromedial prefrontal cortex. Our aim was to examine reward-related decision-making among MDMA users, while considering the influence of other substance use via a poly-drug control group.
Participants and Methods: Abstinent MDMA users ($n = 22$), other drug users ($n = 30$), and healthy non-drug controls ($n = 29$) completed the Iowa Gambling Task (IGT; Bechara et al., 2004), a neuropsychological battery, self-report measures of personality, and a comprehensive drug use interview.
Results: MDMA users and other drug users were similar on measures of cognition and personality; however, both drug use groups demonstrated poorer IGT performance and elevated impulsivity relative to controls. Among MDMA users, individuals who met DSM-IV substance use disorder criteria for MDMA ($n=14$) performed more erratically on the IGT relative to individuals without this diagnosis ($n=8$). Relationships between IGT performance, alcohol and drug use characteristics, and self-report measures of impulsivity were examined using Spearman's correlations.
Conclusions: Both drug use groups were at risk for reward-related decision-making deficits and elevated impulsivity, possibly due to a dysregulated serotonin system and/or ventromedial prefrontal cortex dysfunction. Individuals who abuse or are dependent on MDMA may have a particularly increased risk of executive dysfunction.
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J. JACOBUS, B.C. SCHWEINSBURG, A.D. SCHWEINSBURG, M.J. TAYLOR & I. GRANT. The Interactive Effects of Age and Alcoholism on Brain Response to Spatial Working Memory.
Objective: Previous studies have suggested age-related structural brain changes in alcoholism that differ from effects in normal aging. However, the functional correlates of this relationship have not been well characterized. In this study, we examined the interaction between age and alcoholism on FMRI response during a spatial working memory task, as this task has been shown to be sensitive to alcoholism-related brain injury across a wide age range.
Participants and Methods: Participants were 27 male recently detoxified alcoholics (RDA, abstinent 2 to 3 weeks, mean age = 46.2 ± 8.8) and 11 male controls (mean age = 45.6 ± 9.6) matched on age. FMRI data were acquired while participants performed a 2-back spatial location working memory task. Regression analyses predicted FMRI response from age, alcoholism status, and their interaction.
Results: Groups had similar accuracy and reaction times on the task. FMRI analyses revealed interactions between age and alcoholism in bilateral medial frontal, bilateral superior frontal, and right middle frontal gyri, medial precuneus/posterior cingulate, and bilateral cuneus (clusters > 943 microliters, $p < .05$). Simple effects regressions showed that RDA had a negative relationship between age and FMRI response, while controls showed a positive relationship between age and FMRI response.
Conclusions: These results demonstrate an age-related decline in FMRI response to spatial working memory among alcoholics, yet an age-related increase among controls. In healthy volunteers, neural effort may be increased in older age in order to maintain task performance. Yet in alcoholics, such compensatory responding is observed at a younger age, but this capacity may be limited in older alcoholics. One implication may be that older recently detoxified alcoholics may process information less efficiently, and thus could potentially have difficulty with complex everyday tasks.
Supported by a Veterans Affairs Merit Review Grant to Dr. Grant.
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K. SULLIVAN, P. JANULEWICZ, M. KRENGEL, C. COMTOIS & R. WHITE. Qualitative Findings in Complex Figure Drawing in Military Pesticide Applicators from the Gulf War.
Objective: Current hypotheses for the continued cognitive complaints in GW1 veterans invoke exposure to multiple neurotoxicants. Many neurotoxicants are known to affect the visuospatial domain. Therefore, the goal of this study was to evaluate the relationship of multiple chemical exposures and visuospatial functioning on the Rey-Osterreith Complex Figure Test (ROCFT). By employing the Boston Qualitative Scoring System (BQSS), it was possible to provide an in depth analysis of performance by obtaining 6 summary scores and 17 qualitative scores of the ROCFT.
Participants and Methods: Study participants included a subgroup of 67 GW pesticide control personnel taken from a larger study of GW veterans. Pesticide control personnel were divided into 4 groups based on high and low exposure for pesticides and pyridostigmine bromide (PB). Each study participant completed the ROFCT according to standard administration and standard scoring of the BQSS. It was hypothesized that individuals with multiple chemical exposures (PB, pesticides) would perform significantly worse on the qualitative measures of the BQSS compared with veterans without such exposures.
Results: Multivariate analyses suggested overall group differences on the BQSS configural, cluster, detail, presence, accuracy, placement, and qualitative scores when comparing the four exposure groups of PB and pesticides.
Conclusions: These preliminary findings suggest that multiple chemical exposures in GW pesticide control personnel appear to have resulted in impairments in visuospatial functioning and visual memory as indicated by in depth qualitative scoring of the ROFCT. Further analyses with a larger sample size will help to further elucidate these findings.
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child actors portraying the experience and resolution of problematic social events. For each vignette, participants were prompted to make a judgment as to whether or not they would have responded to the situation in the same way as the protagonist (SIP task), or to monitor the number of children present in the video (control task).
Results: Both children and adults activated similar networks of brain regions during the SIP task, although adults demonstrated greater overall activation in this network compared to children. Adults recruited brain regions hypothesized to be involved in social cognition to a greater extent during the SIP task compared to the control task. In contrast, children recruited largely the same brain regions during the two tasks.
Conclusions: Although both groups activated the same neural network during the SIP task, subtle developmental differences in the brain activation patterns were noted. These differences are likely due to the social situations in the vignettes being more familiar to children, as well as the relative immaturity of cognitive control processes in children.
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K. CHIOU, N. FITZPATRICK, J. WANG, J. VESEK, E. HILLS, D. GOOD & F. HILLARY. **Longitudinal Investigation of Axonal Disruption and its Influence on Brain Activation.**
Objective: Traumatic brain injury (TBI) commonly results in diffuse axonal injury (DAI), which has widespread consequences for neural activity. Diffusion tensor imaging (DTI) can be used to measure white matter integrity and is highly sensitive to identifying DAI. To date, investigators have successfully used DTI to examine common sites of where axonal disruption occurs (e.g., the corpus callosum). However, the relationship between discrete sites of axonal disruption and functional brain activation remains unknown. The complementary use of DTI and functional magnetic resonance imaging (fMRI) can aid in determining the association between local axonal recovery, brain function, and cognitive performance. The influence of axonal recovery was examined longitudinally by examining sites of discrete axonal disruption to determine the influence of axonal recovery on proximal and distal functional brain activation and working memory.
Participants and Methods: Using a Phillips 3T scanner, MRI data were acquired at 3 and 6 months post injury in 5 participants sustaining moderate to severe TBI. FMRI data were collected while subjects performed a visual spatial working memory task. DTI and T2* were used to identify discrete areas of axonal disruption. Fractional anisotropy (FA) maps were co-registered with functional data, and the relationship between FA, BOLD signal change, and reaction time (RT) was examined.
Results: A negative correlation was found between activation and FA values. When comparing the two measurements, RT was positively correlated with change in activation and negatively correlated with change in FA values.
Conclusions: The disruption and recovery of axonal functioning correspond to specific changes in functional brain activation and cognitive performance.
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D.L. MOLFESE, J. SWEATT & F.D. LUBIN. **Long-Lasting Changes In Hippocampus Gene Regulation Following Traumatic Experience.**
Objective: Traumatic experiences can result in lasting memories. While post-traumatic stress (PTSD) is well documented, the underlying cause is unknown.
Participants and Methods: In an animal model of fear memory, rats exposed to footshock in a novel context exhibit freezing (fear) behavior when re-exposed to the same context 24 hours later, indicating they remember the footshock. We examined gene regulation following fear memory. New memories require modifications to histone proteins packaging the DNA.
Results: One hour after footshock, we observed an increase in tri-methylation of Histone H3 at Lysine 4 (H3K4me3) in hippocampus. This modification is associated with gene transcription, a necessary first step in long-term memory formation. Furthermore, when the fear memory was extinguished over 5 days, the increased H3K4me3 persisted, suggesting long-lasting changes in memory regulation from a single traumatic experience. However, when the shock and context were dissociated by pre-exposing the animal to the context prior to shock, we did not observe freezing behavior from animals re-exposed to the context. We also did not observe a change in H3K4me3. We did observe an increase in di-methylation of Histone H3 at Lysine 9 (H3K9me2). This modification is associated with gene suppression, suggesting the prevention of the traumatic memory by dissociating the context from the shock.
Conclusions: These data suggest that traumatic experiences induce long-lasting changes in gene regulation, and consequently in long-term memory. Drug therapies targeting histone-level gene regulation may enable the prevention of PTSD by blocking the molecular cascade necessary for long-term storage of the traumatic memory.
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Invited Symposium

10:45 a.m.–12:15 p.m.

Neuropsychiatric Aspects of Combat Exposure (Blast Injuries, TBI, PTSD)

Chair: Roberta White

R.F. WHITE, K. HEATON, W. RINGE, M. KRENGEL & J. VASTERLING. **Neuropsychiatric Aspects of Combat Exposure (Blast Injuries, TBI and PTSD).**
Symposium Description: Introduction and the experience of deployment. Roberta F. White
This symposium reviews some of the determinants of diminished cognition and affective complaints among military personnel following deployment to combat. Recent findings report that deployment itself is associated with changes in cognition in individuals who are tested both before and after deployment relative to controls tested at similar intervals. This research is briefly reviewed as background to presentations covering the following topics:
Nerve gas agents, neuroimaging and cognition in Gulf War veterans.
New research strategies for the investigation of Gulf War-related illnesses.
Effects of blast injuries among Iraq veterans.
Traumatic brain injury and post-traumatic stress effects in Iraq veterans.
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K. HEATON, S.P. PROCTOR, C.L. PALUMBO, R.J. KILLIANY, D. YURGELUN-TODD, T.C. HEEREN & R.F. WHITE. Neuropsychological and Neuroanatomical Findings in 1991 GW Veterans with Estimated Low-level Exposures to Sarin and Cyclosarin*.

Objective: In March 1991 more than 100,000 US troops were potentially exposed to low levels of the organophosphate nerve agents sarin and cyclosarin following demolition operations at a munitions storage complex at Khamisiyah, Iraq. The structural and functional impacts of low-level exposure to sarin/cyclosarin on the human brain are poorly understood. However, some recent research has indicated subtle, persistent neurobehavioral and neurochemical changes in humans exposed to sarin/cyclosarin at levels insufficient to produce obvious clinical symptoms. In two studies we examined the association between modeled estimates of sarin/cyclosarin exposure levels and neurobehavioral and neuroanatomical outcomes in 1991 Gulf War veterans with varying degrees of possible low-level sarin/cyclosarin exposure. The results of these two studies provide evidence of subtle but persistent central nervous system pathology in Gulf War veterans up to 10 years post-deployment.

*Disclaimer: The views expressed in this presentation are those of the authors and do not reflect the official policy of the Dept of Veterans Affairs, Dept of the Army, Department of Defense, or the U.S. Government.

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W.K. RINGE, C. CULLUM, J. HART, M.T. POSAMENTIER, R.W. BRIGGS & R.W. HALEY. Gulf War Illness Neuroimaging and Biomarker Studies.

Objective: Epidemiological studies at the University of Texas Southwestern Medical Center at Dallas suggest the presence of three distinct syndromes ofGulf War Illness (GWI). Results from neuropsychological testing, magnetic resonance spectroscopy (MRS), and other clinical and genetictests indicate potential basal ganglia dysfunction, in addition to other subtle findings. Here we briefly review these findings and present the design and preliminary results from a current project aimed at longitudinal examination of our original sample as well as extension to a larger randomized sample of GWI subjects. Methods include repeat neuropsychological testing and several functional MRI and EEG protocols designed to target key symptoms of GWI. Additional studies include repeated and extended SPECT cholinergic challenge experiments, MRS, diffusion tensor imaging, and arterial spin labeling MRI, as well as various clinical and genetic tests. The goals of the project are to identify the patterns of brain dysfunction that characterize GWI variants and to develop an accurate, efficient, objective testing strategy for diagnosis.

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M. KRENGEL, K.M. SULLIVAN & L. GRANDE. The Impact of Blast Injury on Cognitive, Psychosocial and Health Outcomes: A preliminary analysis of mild traumatic brain injury in OIF/OEF returnees.

Objective: This presentation summarizes research designed with two aims: 1) to compare cognitive functioning and current health symptoms in Operation Iraqi Freedom/Operation Enduring Freedom veterans with either exposure to blast munitions or non-blast TBI and 2) to evaluate the relationships among health symptoms and diagnostic outcomes in blast exposed versus non-blast exposed mild TBI. Study participants included OIF/OEF returnees with mild traumatic brain injury (TBI). Each participant completed a battery of neuropsychological tests, psychological interviews and health symptom questionnaires. Results of multivariate analyses showed differences in the areas of attention, executive function and short-term memory between the blast injury group and the non-blast TBI group. Results were maintained when controlling for PTSD. In addition, differences were seen in health symptoms between the two groups. The long-term implications of these findings are discussed.

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J.J. VASTERLING, K. BRAILEY & S.P. PROCTOR. The Effects of Mild Traumatic Brain Injury and Exposure to Extreme Stress on Neuropsychological Functioning in the Iraq War: "Shell Shock" revisited?*.

Objective: This presentation discusses neuropsychological outcomes among Iraq-deployed service members who experienced mild traumatic brain injury during deployment. In particular, it addresses the influence of context, including stress exposures, on neuropsychological outcomes. Prospective neuropsychological outcome data obtained as part of the Neurocognition Deployment Health Study serve as the basis for this discussion. Specifically, the presentation incorporates data regarding head injury and PTSD rates in the study sample, and associations found among mild traumatic brain injury, exposure to extreme deployment stress, post-traumatic stress symptoms, and neuropsychological functioning.

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Symposium 8

10:45 a.m.–12:15 p.m.

Predicting Real-World Functioning in at-Risk Populations: The Roles of Everyday Problem Solving and Decision Making Competence.

Chair: Stacey Wood

A. THORNTON & H. KRISTINSSON. Predicting Life Skills Functioning in Patients with Serious Mental Illness.

Objective: The ecological validity of measures of cognition is increasingly recognized as essential to the fields of clinical neuropsychology and psychiatry. Recent developments in everyday problem solving suggest that these measures may be superior to traditional cognitive measures in predicting real-world functional capacities. We report on the extent to which measures of everyday problem solving (EPS) predict daily functioning over and above that of intellectual abilities.

Participants and Methods: The current sample consisted of 22 chronically mentally ill inpatients with psychotic disorders seen at a tertiary psychiatric hospital. Patients underwent interview based measures of psychiatric symptoms (i.e., Signs and Symptoms of Psychiatric Illness; SSPI), nurses' observations of daily functioning (i.e., Routine Assessment of Patient Progress; RAPP), and measures of intellectual functioning (i.e., Kaufmann Brief Intelligence Test – 2nd Edition) and everyday problem solving.

M. KRENGEL, C. COMTOIS, K. SULLIVAN & R.F. WHITE. The Cognitive Correlates of Chronic Multisymptom Illness in GWI Military Pesticide Applicators.

Objective: Exposure to acetylcholinesterase inhibiting pesticides has been advanced as an explanation for the persistent health complaints of the veterans of the Gulf War (GWI). The goal of this study was to evaluate the relationship among pesticide exposure, chronic multisystem illness (CMI) and cognitive functioning of GWI veterans with known exposures. We hypothesized that a high-pesticide exposed group with CMI would show significant cognitive deficits relative to a low-exposed individuals.

Participants and Methods: Participants included a unique group of 100 pesticide control personnel from the GW including pesticide applicators (high-exposed group) and preventive medicine specialists (low-exposed group). Each study participant completed a comprehensive battery of neuropsychological tests and health symptom/exposure assessment questionnaires. Each participant was then categorized as to whether or not they met CDC criteria for CMI based on their responses on the Health Symptom Checklist (HSC) questionnaire. Total health symptoms were also calculated based on the HSC responses.

Results: Chi-square analyses showed that the high-pesticide group was significantly more likely to meet criteria for CMI compared with the low-pesticide group ($p<.01$). Univariate analyses of the HSC scores showed a significant relationship between total health symptoms reported and pesticide exposure categories ($p<.01$). MANOVA analyses showed that total health symptoms were significantly associated with slower response time on CPT mean reaction time and on time to complete the Grooved Pegboard with the non-dominant hand ($p<.01$).

Conclusions: These preliminary findings suggest that GW veterans with high pesticide exposures were more likely to meet self-report criteria for CMI than their low-exposed counterparts. In addition, total number of self-reported health symptoms was also related to pesticide exposure. The higher exposed group reported more total current health symptoms which were correlated with reduced motor skill performance.

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S. KUMBHANI, T. JACOB, D. JIMENEZ, R. ROMERO & J. MOSES. Alcoholism and Familial Vulnerability to Neuropsychological Deficits: A Discordant Twin Study.

Objective: Extensive research has demonstrated cognitive impairments in individuals diagnosed with Alcohol Dependence (AD). However, Children of Alcoholics (COAs), display similar neuropsychological deficits without ever having consumed alcohol. This suggests that some neuropsychological impairment may, in fact, precede the onset of the AD. This study utilized a discordant twin design to address whether or not genetic influences predispose an individual to an AD diagnosis. The main hypothesis is that there would be evidence of familial vulnerability to cognitive deficits. A secondary hypothesis predicted that excessive drinking may have additive executive functioning consequences.

Participants and Methods: This study is based on a 111 twin pair (54 MZ, 57 DZ) sub-sample from the Vietnam Era Twin Registry. Paired-Sample T-Tests and Bivariate Correlations were used to examine the differences between the MZ and DZ groups' performances on the Wisconsin Card Sorting Test (WCST) and Judgment of Line Orientation (JOL). A bivariate linear regression equation was used to test if the more severe drinkers would have higher impairment rates on the WCST.

Results: Results found evidence for the operation of genetic influences on neuropsychological performance. Specifically, no significant difference was found in neuropsychological performance between the co-twins. Additional analyses showed that genetic influences were particularly strong for visuospatial abilities. The results of the linear regression indicated that the severity of AD could not predict the severity of executive function impairment.

Conclusions: Findings were congruent with the literature suggesting that preexisting neuropsychological deficits may predispose individuals to alcoholism vulnerability rather than the observed deficits being solely due to excessive alcohol consumption.

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M.E. MCCABE, P. CHIU & B.P. LANPHEAR. Low Level Lead Exposure and Attention Outcomes.

Objective: Lead is a neurotoxic agent with deleterious effects on developing cognitive function. Even low levels of lead exposure have been shown to negatively impact intelligence (e.g., Canfield et al., 2003). However, less is known about the impact of low levels of lead on neuropsychological domains, such as attention.

Participants and Methods: The present study assessed the impact of blood lead concentration (mean=5.41 µg/dl), measured at 60-months of age, on attention outcomes, assessed at 60- and 66-months, in 176 children, using MANOVA. Attention outcomes, which were nine scales from the Conner's Parent Rating Scale (CPRS; Conners, 1997) and scores from the Map Mission and Opposite World subtests of the Test of Everyday Attention in Children (TEA-Ch; Manly et al., 1999), were entered into a factor analysis using maximum likelihood and oblimin rotation.

Results: A three factor solution emerged as the best explanation for the data; factors were interpreted as: 1) externalizing symptoms (eigenvalue=23.88), 2) selective attention/set-shifting (eigenvalue=3.72), and 3) internalizing symptoms (eigenvalue=2.12). Only participants with blood lead concentrations in the upper and lower thirds of the sample were used for this analysis ($N=122$). A significant group difference was found on the second ($F=13.45$, $p=.0004$) factor, but not on the first nor third.

Conclusions: Children with greater blood lead concentrations had worse selective attention/set-shifting outcomes. These results suggest that even at low levels, lead can affect cognitive function, attention in particular.

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T. MCQUEENY, A.D. SCHWEINSBURG, K.L. HANSON & S.F. TAPERT. Behavioral and Cognitive Impulsivity During Inhibition in Abstinent Adolescent Marijuana Users: An fMRI Study.

Objective: Substance users have shown compromised inhibitory control, the neural substrates of which continue to develop in adolescence. We previously saw subtle neurocognitive decrements among adolescent marijuana (MJ) users, as well as differences in inhibitory processing after a month of abstinence. Here, we examined the relationships between behavioral and neural indicators of inhibitory control in MJ using teens after 28 days of abstinence.

Participants and Methods: Participants (ages 16-19) were 14 MJ teens and 14 demographically similar controls. Adolescents underwent 28 days of abstinence monitored through semiweekly urine toxicology. Participants then completed neuropsychological testing and performed a go/no-go task during functional magnetic resonance imaging (fMRI).

Results: MJ teens did not differ from controls in neuropsychological or go/no-go task performance. However, compared to controls, MJ teens showed more fMRI response in temporal, parietal, occipital, and cerebellar regions, and less response in the inferior anterior cingulate during no-go trials (clusters>1107 microliters, $p<.05$). For controls, better go/no-go accuracy was linked to less activation in left temporal and parietal areas ($p<.05$). However, for MJ teens, go/no-go task performance